THE PHARMACOLOGICAL MANAGEMENT OF AUTISM SPECTRUM DISORDER IN CHILDREN.

SUBMITTED TO THE

DISCIPLINE OF PHARMACEUTICAL SCIENCES

SCHOOL OF HEALTH SCIENCES

UNIVERSITY OF KWAZULU-NATAL

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As the dissertation component in fulfilment for the degree; Master of Pharmacy;

University of KwaZulu-Natal

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Co-Supervisor: Ms Saira Banu Karrim

Preface

This dissertation is presented in a manuscript format. The findings of the study are presented in chapters two and chapter three as manuscripts, as required by the regulations of the University of KwaZulu-Natal. The systematic review manuscript in chapter two was submitted for publication to the journal, Neuropsychiatric Disease and Treatment. The review was accepted for publication and published online (6th August 2022) and also indexed on PubMed (25th August 2022). The manuscript in chapter three has been submitted for publication to the journal, Child Psychiatry and Human Development and is still under editorial review. The references used in the manuscripts were cited according to the instructions/ guidelines for authors as required by the journals.

This dissertation consists of four chapters as described below:

Chapter 1: Provides an introduction and explains the rationale and significance of the study. The aims, objectives, and methodology of the study are also presented.

Chapter 2: Manuscript I entitled, "The Pharmacological Management of Core Symptoms and Comorbidities of Autism Spectrum Disorder in Children and Adolescents": A Systematic Review was written according to the author's guidelines and published by the journal, Neuropsychiatric Disease and Treatment.

Chapter 3: Manuscript II entitled, "An Overview of Pharmacotherapy in the Management of Children with Autism Spectrum Disorder at a Public Hospital in KwaZulu-Natal" was written according to the author guidelines and submitted for publication to the journal, Child Psychiatry and Human Development.

Chapter 4: This chapter provides a summary of the findings, future recommendations, limitations, strengths of the study and conclusion.

Declaration 1: Dissertation submission

This is to certify that the contents of this dissertation are the original work of:

Student: Jennal Maniram (200303093)

Signed: 

Date: 07/11/22

As the student's supervisor and co-supervisors, we have approved this dissertation for submission.

Supervisor: Professor Frasia Oosthuizen

Signed: _____

Date:

Co-Supervisor: Ms Saira Banu Karrim

Signed: _____

Date:

Declaration 2: Plagiarism

I, **Jennal Maniram**, declare that:

1. The research reported in this dissertation, except where referenced, is my original work.

2. This dissertation has not been submitted for any degree or examination at any other university.

3. This dissertation does not contain other persons' data, pictures, graphs, or other information unless specifically acknowledged as being sourced from other persons.

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a. their words have been re-written but the general information attributed to them has been referenced.

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This is to certify that the contents of this thesis are the original work of Miss Jennal Maniram and as the candidate's supervisor/ co-supervisors, I have approved this thesis for submission.

Signed: Professor Frasia Oosthuizen: _____ Date:

Ms Saira Banu Karrim: _____ Date:

Declaration 3: Ethical approval

Ethical approval for this study was obtained from the Biomedical Research and Ethics Committee (BREC) at the University of KwaZulu-Natal (UKZN). Reference number: BREC/00003667/2021 - Annexure 1.

Permission to conduct this study was approved by the KwaZulu-Natal Department of Health (KZN DoH). Reference number: KZ_202112_018 - Annexure 2.

Permission for the retrieval of data and access to KZN Children's hospital was obtained from the EThekwini Health District – Annexure 3.

Declaration 4: Manuscript publication

My contribution to the project was as follows:

Jennal Maniram: Author – responsible for performing all literature reviews, data, and statistical analyses, interpretation of the results, manuscript preparation and submission to journals, liaising with editorial team members, and preparation of the dissertation.

The contributions of others to the project were as follows:

Professor Frasia Oosthuizen: Supervisor – supervision of the concept of the study, the review, and editing of both manuscripts and dissertation.

Ms. Saira Banu Karrim: Co-Supervisor – review, and editing of both manuscripts and dissertation.

Dr Ebenezer Wiafe: Review, and editing of manuscript I.

Dedication

I dedicate this project to my nephew Nathan, who was diagnosed with a severe form of autism spectrum disorder at the age of two. The difficult challenges he faces daily as an autistic child motivated me to embark on this project to gain clarity on the role of pharmacotherapy in the management of autism and to promote awareness of my research findings to health care professionals, parents and caregivers that deal with children diagnosed with autism. I also dedicate this project to the Lord Jesus Christ and my parents who have been my pillar of strength throughout my academic and professional career.

Acknowledgements

The author of the project would like to acknowledge and express thanks to the following people who have assisted and contributed to the completion of the dissertation.

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Dove Medical Press and the Journal of Neuropsychiatric Disease and Treatment - Thank you for accepting manuscript I for publication.

List of acronyms and abbreviations

AAC	Augmentative and Alternative Communication
ABC	Aberrant Behaviour Checklist
ABFW	Child Language Test in Phonology, Vocabulary, Fluency, and Pragmatics
ADHD	Attention Deficit Hyperactivity Disorder
ADL	Activities of Daily Living (Language Development Assessment)
ADOS	Autism Diagnostic Observation Schedule
ASD	Autism Spectrum Disorder
ATX	Atomoxetine
AVP	Vasopressin
BREC	Biomedical Research and Ethics Committee
CARS	Childhood Autism Rating Scale
CDC	Centers for Disease Control and Prevention
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression -Improvement
CI	Confidence Interval
CYBOCS-ASD	Children's Yale-Brown Obsessive-Compulsive Scale-Modified for Autism Spectrum Disorder
CYBOCS-PDD	Children's Yale-Brown Obsessive-Compulsive Scale-Modified for Pervasive Developmental Disorder
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

FDA	Food and Drug Administration
FERT	Facial Emotion Recognition Test
FRAA	Folate Receptor-α Autoantibody
GABA	Gamma-Aminobutyric Acid
GARS-2	The Gilliam Autism Rating Scale-second edition
GI	Gastrointestinal
JBI	Joanna Briggs Institute
KZN-DOH	KwaZulu-Natal Department of Health
MMRS	Mixed-Methods Systematic Reviews
NAC	N-Acetyl cysteine
OCD	Obsessive Compulsive Disorder
OM	Omega Fatty Acid
p	probability
PEA	Palmitoylethanolamide
PRISMA	The Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PT	Parent Therapy
PTP	Parent Target Problem
RBS-R	Repetitive Behaviour Scale–Revised
RMET	Reading the Mind in the Eyes Test
SD	Standard Deviation
SED	Subclinical Epileptiform Discharges
SNAP	Swanson, Nolan, and Pelham Teacher and Parent Rating Scale

SPSS	Statistical Package for the Social Sciences
SRS	Social Responsive Scale
SSRI	Selective Serotonin Reuptake Inhibitor
UKZN	University of KwaZulu-Natal
USA	United States of America
WHO	World Health Organization
VI	Vitamin D
VIDOM	Vitamin D and Omega Fatty Acids

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Abstract

Background

Autism Spectrum Disorder (ASD) is a developmental disorder that affects individuals from early childhood. The pharmacological management of ASD in children remains a challenge due to limited effective management options and the absence of approved drugs to manage the core symptoms. This study aimed to review pharmacological treatment options used in the management of ASD in children at a public hospital in KwaZulu-Natal by identifying pharmacological agents prescribed and determining the role and impact on treatment outcomes. Additionally, the study aimed to review effective pharmacological management options employed in managing the core symptoms and comorbidities of ASD on an international scale by conducting a systematic review.

Method

A quantitative retrospective study was conducted by reviewing patient files of children diagnosed with ASD, meeting the inclusion criteria. A descriptive analysis was done to identify prescribing trends and therapeutic outcomes.

A systematic review was also conducted to identify pharmacotherapeutic options for the management of ASD in children and adolescents. A systematic search for studies from January 2012 to January 2022 was performed using four databases, which included: PubMed, Scopus, Science Direct, and PsycInfo. A narrative synthesis was used for data analysis.

Results

A total of 181 children met the inclusion criteria for the study. Risperidone was the most frequently prescribed drug (88%) for the management of comorbidities and/or core symptoms of ASD. Attention deficit hyperactivity disorder (54%), irritability or aggression (25%), and

sleep dysregulation (22%) were frequent ASD comorbidities that warranted pharmacotherapy. Drugs prescribed to manage ASD comorbidities included methylphenidate, melatonin, sodium valproate, risperidone, oxybutynin, carbamazepine, and others. Risperidone and non-pharmacological therapies played a prominent role in targeting the core symptoms of ASD. In 41% of patients, there was a positive response to treatment and 20% of patients experienced improvements in the core symptoms of ASD.

The systematic review provides a comprehensive list of effective management options for ASD comorbidities and core symptoms from 33 included studies. Risperidone, aripiprazole, methylphenidate, guanfacine, levetiracetam, and atomoxetine are examples of effective pharmacological drugs against ASD comorbidities. Effective drugs for the management of ASD core symptoms include but are not limited to, bumetanide, fluoxetine, intranasal oxytocin, intranasal vasopressin, and prednisolone.

Conclusion

Pharmacotherapy plays an important role in managing the comorbidities of ASD, however, the use of drugs in the management of ASD core symptoms is limited at the public hospital in KwaZulu-Natal. The systematic review successfully summarised the pharmacological advancements made in the past decade and includes promising therapeutic options that manage the core symptoms and comorbidities of ASD.

Chapter 1: Introduction

This chapter presents the research proposal and overall outline of the study. It includes the background, literature review, problem statement, rationale and significance of the study. Additionally, the study aims, objectives and methodology for both manuscripts are highlighted and discussed.

1.1 Background

Autism spectrum disorder (ASD) is a complex developmental condition that involves persistent challenges in social interaction, verbal and nonverbal communication, and restricted/repetitive behaviours (American Psychiatric Association, 2018). Although most causes of ASD remain unknown, possible factors include children born to older parents, prenatal exposure to environmental toxins and heavy metals, family history, genetic mutations and disorders, premature birth, and chemical and metabolic imbalances (Holland, 2021). Autism also tends to occur more frequently than expected among individuals who have certain medical conditions, including fragile X syndrome, tuberous sclerosis, congenital rubella syndrome, and untreated phenylketonuria (Autism Society, 2015). According to a report from the World Health Organization (WHO), it has been estimated that one in 160 children worldwide has ASD and this figure could be substantially higher because the prevalence of ASD in many low and middle-income countries remains unknown (World Health Organisation, 2021). In South Africa, accurate local statistics for ASD are not available but it has been estimated that between 1% and 2% of the population may be affected by ASD (Autism South Africa, 2021).

The Diagnostic and Statistical Manual of Mental Disorders (DSM–5) (American Psychiatric Association, 2013) is now the standard reference that healthcare providers use to diagnose mental and behavioural conditions, including ASD. To meet diagnostic criteria for ASD according to DSM-5, a child must have persistent deficits in each of three areas of social communication and interaction plus at least two of four types of restricted, repetitive behaviours. DSM-5 criteria include three severity classifications for ASD which include Level 1 (requiring support), Level 2 (requiring substantial support), and Level 3 (requiring very substantial support) (American Psychiatric Association, 2013).

The core symptoms of ASD become noticeable during early childhood (between 12 and 24 months of age) and are divided into two categories:

- Problems with communication and social interaction including difficulties sharing emotions, sharing interests, or maintaining a topic or turn taking in a conversation, issues with nonverbal communication, such as difficulty maintaining eye contact or reading body language, difficulties developing and maintaining relationships

- Restricted or repetitive patterns of behaviour or activities (repetitive movements, motions, or speech patterns, rigid adherence to specific routines or behaviours, an increase or decrease in sensitivity to specific sensory information from their surroundings, such as a negative reaction to a specific sound, fixated interests or preoccupations) (Cherney, 2019).

A range of medical comorbidities frequently accompany individuals with ASD and include gastrointestinal problems, epilepsy, feeding issues, disrupted sleep, attention-deficit/hyperactivity disorder (ADHD), anxiety, depression, obsessive-compulsive disorder (OCD), schizophrenia, and bipolar disorder (Autism Speaks, 2021).

Non-pharmacological measures to manage ASD include applied behaviour analysis, social skills training, occupational therapy, physical therapy, sensory integration therapy, speech-language therapy, and the use of augmentative and alternative communication (AAC) (Centers for Disease Control and Prevention, 2019b). Currently, there are no pharmacological treatments that can cure ASD; however, pharmacotherapy can assist in the management of certain symptoms associated with ASD. The Food and Drug Administration (FDA) has approved the use of two antipsychotic drugs, risperidone, and aripiprazole, for treating irritability associated with ASD in children (National Institutes of Health, 2021). There is little evidence that any of the current pharmacotherapy options appreciably improves the symptoms of ASD, therefore there is a great need for research into the long-term benefits and risks of pharmacotherapy in autism (Gibbs, 2010).

1.2 Literature Review

1.2.1 The Role of Pharmacological Therapy in the Management of ASD

The treatment of ASD requires a multimodal approach with a multidisciplinary team that targets core behaviours, improves social interaction and communication, and reduces disruptive behaviour (Shenoy et al., 2017). The most effective treatments available today for the management of ASD are:

- Behavioural management therapy
- Cognitive behaviour therapy
- Educational and school-based therapies
- Joint attention therapy
- Pharmacotherapy
- Nutritional therapy
- Occupational therapy
- Parent-mediated therapy
- Physical therapy
- Social skills training and
- Speech-language therapy (National Institute of Child Health and Development, 2021).

A study that aimed to evaluate, compare and rank the therapy techniques used in the management of ASD indicated that applied behavioural analysis, cognitive behavioural therapy, and speech-language therapy are the most preferred techniques, followed by the pharmacological use of aripiprazole and risperidone (Ozsahin et al., 2021).

Pharmacotherapy is employed in treating patients with ASD to augment responses to behavioural and educational interventions as well as improve overall functioning (Palermo, 2004). Drug treatment may not be effective for the core symptoms of ASD, however, it may have a role in managing comorbidities and related symptoms, such as irritability and aggression (Turner, 2020). Pharmacological therapy also assists in managing high energy levels, the inability to focus, anxiety and depression, behavioural reactivity, self-injury, and seizures (Centers for Disease Control and Prevention, 2019a).

1.2.2 Currently Approved Drugs for ASD

Risperidone and aripiprazole are currently the only medications approved by the FDA for symptoms associated with ASD, specifically targeting the irritability often seen with this diagnosis (DeFilippis, 2016). Risperidone, an atypical antipsychotic agent, has demonstrated considerable benefits in reducing several behavioural symptoms associated with ASD (Sharma et al., 2012). Risperidone is effective for short-term treatment of aggression, temper outbursts, and self-injurious behaviour in children with autism (Hyman, 2002). Atypical antipsychotic agents, which block postsynaptic dopamine and serotonin receptors, have advantages over traditional antipsychotic medications in the treatment of adults with schizophrenia and may be

beneficial in children with autistic disorder who have serious behavioural disturbances (McCracken et al., 2002). From a pharmacological perspective, aripiprazole is different from other antipsychotic agents, as it is the only approved antipsychotic that reduces dopaminergic neurotransmission through D2 partial agonism (Shapiro et al., 2003). Aripiprazole was approved by the FDA to treat irritability in children and adolescents with autistic disorder aged 6–17 years (Blankenship et al., 2010).

A Bayesian meta-analysis of efficacy and secondary effects of risperidone and aripiprazole revealed that risperidone and aripiprazole are equally effective for behavioural disturbances of ASD but adverse effects are frequent and include weight gain, sedation, and extrapyramidal symptoms (Cohen et al., 2013). A case study done in Dubai showed promising results for aripiprazole and risperidone as improvement was observed in ASD core signs and symptoms. This is the first study to suggest that ASD can potentially be treated in very young children (<4 years), however, clinical trials are urgently required to validate these findings among the paediatric population (Alsayouf et al., 2021).

Apart from risperidone and aripiprazole, other classes of medicine that are effective in improving behavioural symptoms of ASD, include neurotransmitter reuptake inhibitors (i.e. fluoxetine), tricyclic antidepressants (i.e. imipramine), anticonvulsants (i.e. lamotrigine), atypical antipsychotics (i.e. clozapine), and acetylcholinesterase inhibitors (i.e. rivastigmine) (Kumar et al., 2012).

1.2.3 Psychotropic Drug Use in the Management of ASD

Psychotropic drugs which act by adjusting levels of neurotransmitters, like dopamine, Gamma-Aminobutyric Acid (GABA), norepinephrine, and serotonin, are divided into five classes including anxiolytics, antidepressants, antipsychotics, mood stabilizers, and stimulants (Ghoshal, 2019). These drugs play an important role in the pharmacological management of ASD for the treatment of non-core symptoms and psychiatric comorbidities (Jobski et al., 2017).

A systematic review of pharmacotherapy for ASD indicated that several classes of psychotropic medications have been used to decrease the wide range of “maladaptive” or “interfering” behaviours and associated medical problems that can hinder the implementation of various non-pharmacological interventions. Atypical neuroleptics was shown to be useful in the treatment of behavioural symptoms of ASD while attention deficit and hyperactivity

disorder medications may be effective for counteracting the additional features of hyperactivity and short attention span (Benvenuto et al., 2013).

A study in the USA that reviewed the efficacy of methylphenidate (a stimulant) among children with ASD and symptoms of ADHD found a decrease in ratings of stereotypy and inappropriate speech, which are often associated with core autistic features; however, significant adverse side effects like social withdrawal and irritability were noted (Handen et al., 2000). Results from a randomised clinical trial that involved the use of the antidepressant, fluoxetine, among children and adolescents with ASD, indicated that treatment with fluoxetine compared with placebo resulted in significantly lower scores for obsessive-compulsive behaviours (Reddihough et al., 2019). Similarly, other psychotropic drugs like clozapine (Yalcin et al., 2016) and atomoxetine (Harfterkamp et al., 2009) have shown positive results in ASD; however, there is a need for further studies to demonstrate clinical efficacy.

The absence of gold standard treatment for ASD, limited clarity on ASD management guidelines, and insufficient evidence-based pharmacological interventions, other than for aripiprazole and risperidone, increases the risk of off-label prescribing and adverse effects among individuals with ASD (Vohra et al., 2016).

1.2.4 The Evaluation of the Pharmacological Management of ASD Internationally and in South Africa.

A study to investigate psychotropic drug prescribing patterns for ASD treatment in children and adults in Europe (France, Germany, Italy, Spain, and the United Kingdom), South America (Mexico and Brazil), North America (Canada and United States of America), and Asia (Japan) revealed that, apart from risperidone being most commonly prescribed, methylphenidate and haloperidol was also used extensively in young persons with ASD. This study concluded that there was a lack of consistency in medication use for ASD. This could be due to differences in diagnostic criteria, clinical guidelines, or health care systems. This study also highlighted the lack of evidence on safety and efficacy for many of the drugs prescribed, therefore more research is warranted (Hsia et al., 2014).

A similar study that assessed the variation of psychopharmacological prescription rates in 30 countries found that the highest prescription rates for medication to treat ASD were found in Western Europe while the lowest prescription rates were found in countries such as Turkey, Indonesia, Saudi Arabia, and Pakistan. The most commonly prescribed medication for ASD was risperidone, however, antidepressants and antiepileptic drugs were also frequently

prescribed. The marked differences between prescription rates in different countries could be related to economic factors; countries with a higher GDP were found to have higher prescription rates (Wong et al., 2014).

A recent study documenting the use of psychotropic medication in Iranian children diagnosed with ASD provided interesting results. Upwards of 80% of children with ASD were prescribed psychotropic medication, with around one-quarter of children taking two or more medications. Medication use was also higher among male children showing difficult-to-manage behaviours such as hyperactivity. The study concluded that multi-disciplinary, behavioural, therapeutic, and educational interventions, which are required for the management of ASD, are not widely available in Iran, although a start has been made (McConkey et al., 2021).

The only study in South Africa that assessed prevalence and patterns of medication use in children with ASD were conducted at two schools for children with ASD in Cape Town and the Autism Action database. A survey questionnaire and the Nisonger Child Behaviour Rating Form were administered to parents of children and adolescents. This study found a total of 24.6% of children used psychotropic medications with antipsychotics the most commonly used. Stimulants, antidepressants, and mood stabilizers were also prescribed. Complementary and alternative medications were commonly used with 40% of children using over-the-counter medications and 15.4% being on a special diet for autism (Louw et al., 2012).

There is a need for more research to be conducted in the field of pharmacological treatment options for ASD. Research on the pharmacological management of ASD should ideally target treatment for the core symptoms of ASD as well as ASD-related comorbidities. Most of the current studies that evaluate the pharmacological management of ASD are either done in a short time frame, involve a small number of participants, evaluate only psychotropic medication use, or have limited information on individual drug efficacy. There are also limited studies that evaluate the pharmacological management of ASD in Africa. This study is the first known study in done in the public healthcare sector in KwaZulu-Natal to evaluate the pharmacological management of ASD.

1.3 . Problem Statement

The pharmacological management of ASD remains a challenge and with FDA approval of only two drugs to treat some of the symptoms, it is apparent that more research is warranted in this area. There is limited research on the pharmacological management of ASD in South Africa and Africa as a continent, notwithstanding the increasing number of children diagnosed with

this condition. It remains questionable if there will ever be a cure for children with ASD, however, additional research on pharmacological treatment options could facilitate more positive therapeutic outcomes.

1.4 Rationale and Significance of this Study

An overview of prescribing patterns of pharmacotherapy in the management of ASD might provide insight into current management practice and possibly identify areas of concern. In South Africa, the only known study that describes patterns of pharmacological treatments for ASD was done nine years ago in the Western Cape (Louw et al., 2012); therefore, current research is required to provide insight on medication use in South Africa for ASD.

A systematic review of literature on the pharmacological management of ASD on an international scale will outline advancements in research and how this can be applied in South Africa and will also provide increased awareness when utilising pharmacotherapy as a treatment option for ASD. Due to the growing prevalence of ASD in South Africa and the urgent necessity to find effective treatments for the core and associated symptoms of ASD, a study of this nature can assist to identify the role of pharmacotherapy in a public hospital in KwaZulu-Natal and possibly be extrapolated to the South African situation.

1.5 Research Questions

1.5.1 What are the current trends internationally with relation to the pharmacological management of ASD?

1.5.2 What role does pharmacotherapy play in the management of ASD in a public healthcare facility in KwaZulu-Natal?

1.5.3 How does the pharmacological management of ASD impact on treatment outcomes?

1.5.4 How does the pharmacological management used in a public healthcare facility in KwaZulu-Natal compare to international trends?

1.6 Aim and Objectives

Aim: This study aims to review pharmacological treatment options used in the management of ASD in children.

Objectives:

1. To conduct a systematic review of current pharmacological management options for ASD.
2. To retrospectively review drugs used in the management of children with ASD at a public hospital in KwaZulu-Natal.
3. To identify the most common ASD comorbidities that require pharmacological treatment.
4. To review therapy outcomes in children with ASD receiving pharmacological management.

1.7 Methodology

1.7.1 Study Design

Systematic Review

A systematic review has been performed to determine the role of pharmacotherapy in the management of ASD. A systematic search for studies from the year 2012 to 2022 was performed using four databases, including PubMed, Scopus, PsycInfo and Science Direct. The systematic review involved the categorisation of data into relevant sections and subsections depending on research done for the pharmacological management of the core symptoms of ASD, the pharmacological management of ASD-related comorbidities, novel pharmacological treatment options as well as drug target development pathways for ASD. The Joana Briggs Institute (JBI) guidelines for Mixed-Methods Systematic Reviews (MMSRs) and the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines were followed (Joanna Briggs Institute, 2021).

ASD Pharmacotherapy Review

A retrospective descriptive study was carried out to determine the pharmacological management of children diagnosed with ASD at a public hospital facility in KwaZulu-Natal. Medication use was obtained from patient charts reviewed at the facility. Comorbidities and the role of pharmacotherapy in these comorbidities as well as the outcome of therapy was extracted from patient charts.

1.7.2 Study Setting

The study setting was a public hospital facility located in KwaZulu-Natal. The public hospital used in this study was initially built in 1928 as the first facility in Africa dedicated exclusively

to the treatment of children. Although the hospital closed in 1984 for 28 years under the apartheid government, local leaders began on a restoration and rebuild process of the old hospital and it now provides extensive, impartial healthcare and support to children and youth. The hospital is also home to a neuro-developmental assessment centre and specialised paediatric neurologists that manage children diagnosed with ASD.

1.7.3 Study Target Population and Sampling Strategy

Inclusion Criteria

The following criteria were used to select patient files for inclusion in the study:

- Male and female individuals diagnosed with ASD (on all levels of severity of the DSM 5).
- Children and adolescents between the age group of 2 and 17 years of age since most symptoms of ASD manifest before the age of 3 years and some symptoms improve with age and proper management of the condition (CDC, 2021).
- All ASD individuals with hospital visits from January 2019.
- ASD individuals will all types of medical comorbidities.

Exclusion Criteria:

- Paediatric neurology patients who are not on the autism spectrum.
- ASD patients who are not prescribed any type of medication to manage the condition.
- All individuals over the age of 17 since this study is an evaluation of the pharmacological management of ASD in children.

1.7.4 Sample Size

Sample selection included all patients that met the inclusion criteria mentioned above. Due to the retrospective nature of the study, a predetermining sample size was not possible. A total of 181 patients did meet the study inclusion criteria.

1.7.5 Data Source

Patient medical files were the primary data source used. The following information were extracted: name of drug, age, gender of patient, dose, and frequency of the drug/s prescribed, and the date of initial diagnosis.

The prescriber's notes on the patient's progress was obtained from the patient medical records to determine the effectiveness of treatment. Any change in the patient's condition related to the DSM-5 level of severity was recorded. An improvement or decline in the patient's condition that was noted on the patient's file was noted as an indicator of the therapeutic outcome on the management of ASD.

ASD-related comorbidities that warrant treatment pharmacologically were determined from the patient's file and also by identification of the class of drug prescribed to treat a particular condition. The results obtained from the retrospective study are compared to international trends in pharmacological management.

1.7.6 Data Collection Tool

A data extraction template (Appendix 1) was also utilised to obtain information that was required for the systematic review. This template was designed to record information related to the name of the author, publication year, country, setting, study design and title, name of the medication, demographic description, sample size, and main findings.

A data extraction template (Appendix 5) was utilised to enter all required information for the retrospective study. The age, gender, and information related to name, dose, and frequency of medication/s prescribed were included on the template. The selected patient demographics (age and gender) are important to identify predictors and prevalence patterns associated with the use of a particular type of medication while the pharmacological information required, aided in documenting the use of different classes of medication among children with ASD as seen in previous international studies like (Guifeng et al., 2019; McConkey et al., 2021). The template also included the date of initial diagnosis, non-pharmacological interventions, and therapeutic outcomes to determine treatment effectiveness. Additionally, medical comorbidities were included in the data extraction tool to identify the most common conditions that warrant pharmacotherapy.

1.7.7 Data Analysis

Data was analysed by descriptive statistics using the Statistical Package for the Social Sciences (SPSS). Data is presented in the form of frequency tables, bar graphs, pie charts, and prevalence proportions. Statistical tests example the t-test was utilised to determine the probability or statistical significance of results obtained when required.

1.7.6 Data Management

All data collected is stored on a password-protected laptop device. After a period of at least 5 years, all data will be removed from the device.

1.7.8 Data Confidentiality and Ethical approval

To maintain confidentiality, no information that could identify patients was extracted during the data collection process. As this study obtained information from patient files, with no direct contact with patients, informed consent was not needed. Ethical approval was obtained from the Biomedical Research and Ethics Committee (BREC), UKZN (Reference number - KZ_202112_018) and the KZN Department of Health (KZN-DOH). Consent for access to the patient files was sought from the Medical Management of the public hospital which is managed from the district office of KZN. Ethical clearance for the systematic review was not required.

1.8 Conclusion

To be trapped in a world where one is unable to communicate verbally or express oneself emotionally, have limited physical interactions with others, and still encounter a range of medical comorbidities simultaneously are some of the challenges faced by children with ASD daily. The pharmacological management of ASD has always presented a challenge due to the few effective treatment options and the absence of drugs that can cure the core symptoms. This study is the first to be conducted in KwaZulu-Natal, South Africa, and one of the limited international studies. As custodians of medication, pharmacists can play an active role in the evaluation of pharmacotherapy for ASD, promote awareness of the condition to patients and other health care professionals as well as research new developments related to the pharmacological management of ASD.

Chapter summary

This chapter outlines the overall context of the study to be conducted. This included a discussion on the study aims, objectives and methodology. The following chapter is based on the pharmacological management of core symptoms and comorbidities of ASD in children and adolescents and was conducted as a systematic review.

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Chapter 2: Manuscript I

Introduction

Pharmacological management options for the core symptoms and comorbidities of ASD are highlighted and discussed in chapter 2. This was done by conducting a systematic review based on randomized clinical trials for drugs with positive therapeutic outcomes on ASD management over the past decade. Chapter two is in manuscript format in accordance with the College of Health Sciences guidelines for dissertation submission at the University of KwaZulu-Natal (UKZN). This chapter is presented as a systematic review and was submitted to the Journal of Neuropsychiatric Disease and Treatment and was accepted for publication (Annexure 4). The systematic review was also formatted, written and referenced according to author guidelines for the chosen journal which can be viewed in Annexure 5. The systematic review was published online on the 6th August 2022 and was indexed on PubMed on the 25th August 2022; DOI https://doi.org/10.2147/NDT.S371013.

2.1 Systematic Review Protocol

Title

The Pharmacological Management of the Core Symptoms and Comorbidities of Autism Spectrum Disorder in Children and Adolescents: A Systematic Review.

Short Title

Pharmacotherapy of the Core Symptoms & Comorbidities of Autism in Children and Adolescents.

Authors

Jennal Maniram; Saira Karim; Frasia Oosthuizen; Ebenezer Wiafe.

Keywords: Autism Spectrum Disorder, Children and Adolescents, Pharmacotherapy, Comorbidity, Core Symptoms, Drug Treatment, Systematic Review

Abstract

Background: Autism Spectrum Disorder (ASD) is a delayed developmental disorder that affects individuals from early childhood. In June 2021, the World Health Organisation (WHO) had estimated that ASD affects approximately one in 100 children worldwide. The core symptoms of ASD, which include impairments in social skills (interaction and communication) and restricted and repetitive behaviours, have always posed a challenge to medicine due to the absence of approved pharmacological treatment options. Additionally, beneficial pharmacotherapy is also required for the management of ASD comorbidities. To date, the only drugs approved to treat irritability and aggression seen in ASD patients, include risperidone and aripiprazole. Research on additional effective pharmacological treatment options for ASD and its comorbid conditions is crucial to facilitate improved therapeutic outcomes.

Methods: A search of medical databases, PubMed, Scopus, Science Direct, and PsycInfo for pharmacological treatment options for ASD will be conducted; studies from January 2012 to January 2022 will be included. The search will be limited to studies published in the English language and will include all studies that meet the inclusion criteria. Duplication of studies will

be removed by utilising the EndNote citation manager. Citations will be screened independently by two authors. Narrative synthesis, will be used for data synthesis.

Ethics and dissemination: This study will not include primary data collection; therefore, formal ethical clearance will not be required. The results of the study will be presented in a peer-reviewed journal. Additionally, results will be disseminated to health facilities that deal with children presenting with ASD.

Patient and public involvement: Patients or the public will not be involved in the conduct of this study.

Background and Rationale

Autism Spectrum Disorder (ASD) is a complex, lifelong developmental disability that typically appears during early childhood and can impact a person's social skills, communication, relationships, and self-regulation. Autism is defined by a certain set of behaviours and is a "spectrum condition" that affects people differently and to a varying degree (Autism Society, 2020).

The core symptoms of ASD include social communication and social interaction challenges and restricted or repetitive behaviours or interests. ASD individuals also present with a range of comorbidities which include, but are not limited to, delayed cognitive or learning skills, hyperactivity, impulsivity, and/or inattentive behaviour, epilepsy or seizure disorder, unusual eating and sleeping habits, gastrointestinal issues (e.g., constipation), unusual mood or emotional reactions and anxiety, stress, or excessive worry (Centers for Disease Control and Prevention, 2021).

Although there is little evidence that any medication reliably relieves the core symptoms of ASD to a major degree, most patients receive some form of pharmacotherapy, much of it off-label, with the primary therapeutic aim being to improve participation during behavioural and educational therapies(Gibbs, 2010). Risperidone and aripiprazole are currently the only medications that the Food and Drug Administration (FDA) has approved for symptoms associated with ASD targeting the irritability often seen with this diagnosis (DeFilippis et al., 2016).

Psychotropic drugs, which work by adjusting levels of neurotransmitters like dopamine, gamma-aminobutyric acid (GABA), norepinephrine, and serotonin, are divided into five

classes which include anti-anxiety agents, antidepressants, antipsychotics, mood stabilizers, and stimulants (Ghoshal, 2019). These drugs play an important role in the pharmacological management of ASD to treat non-core symptoms and psychiatric comorbidities (Jobski et al., 2017).

Drug treatment should always be part of a comprehensive management plan that includes behavioural and educational interventions and should be focused on specific targets (Benvenuto et al., 2013).

Previous international systematic reviews regarding the pharmacological management of ASD in children either involved an investigation of pharmacological interventions for the core symptoms of ASD only (Clevenger et al., 2021) or involved a systematic review of psychotropic drug use for ASD comorbidities (Persico et al., 2021).

There is an urgent need for more research to be conducted on the pharmacological management of ASD considering there are currently only 2 drugs with FDA approval to assist with irritation and aggression. There are also no known approved treatments for the core symptoms of ASD. The pharmacological management of ASD should ideally incorporate drugs that improve the core symptoms of ASD as well as assist in managing comorbidities in children. This will lead to enhanced therapeutic outcomes and improved quality of life for children with ASD. This systematic review presents an investigation on the pharmacological management of the most common health challenges encountered by children with ASD and will assist in the following areas of interest:

- The identification of drugs that can assist to manage the core symptoms of ASD.
- The identification of pharmacological agents that assist in managing the various types of comorbidities experienced by children with ASD.
- The therapeutic outcomes from all studies included in the review.

Review questions

1. What pharmacological options are available to manage the core symptoms of ASD in children and adolescents?
2. What are the current treatment options for the pharmacological management of ASD-related comorbidities in children and adolescents?

3. What are the therapeutic outcomes of pharmacological treatments employed in the management of ASD core symptoms and comorbidities in children and adolescents?

Aim

This study aims to systematically review potential options for the pharmacological management of ASD in children and adolescents by identifying treatments for the core symptoms and comorbidities of ASD. The study will also investigate and review the effectiveness of treatment options for ASD.

Objectives

1. To develop a comprehensive list of pharmaceutical agents that are in use for the management of the core symptoms of ASD.
2. To identify available pharmacological options for the management of ASD-related comorbidities.
3. To review and discuss therapeutic outcomes of all studies included in this review.

Methodology

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (2020) for systematic reviews will be followed from design to reporting.

Eligibility Criteria

Inclusion Criteria

The PICO framework will be used to determine the eligibility of this study.

- P- Population/ participants: Children and Adolescents (male and female) diagnosed with ASD (Autistic Disorder, Asperger's Syndrome, or Pervasive Development Disorder) and between the ages of 2 and 18 years old.
- I- Intervention: Pharmacological Management of Autism (will also include vitamin, dietary, or mineral supplements when used for medicinal purposes to treat the core symptoms or an ASD comorbidity)
- C- Comparison: studies where the pharmacological treatment is compared to placebo, no treatment, a different drug, or non-pharmacological therapy.
- O- Outcome: An outcome measure that results in an improvement in the core symptoms of ASD and/or ASD comorbidity.

Exclusion studies

- Non-English studies.
- Studies not having the outcome of interest.
- Studies before the year 2012 and after 01 January 2022
- Studies that are not randomised control trials

Types of studies

This systematic review will include quantitative studies since an improved outcome measure based on numerical data is required. Quantitative studies will include only randomised control trials.

Main Outcomes

- The pharmacological management of the core symptoms of ASD.
- The pharmacological management of ASD comorbidities.

Secondary Outcomes

- The identification of treatment outcomes from all studies included in the review.

Information sources

A comprehensive search will be conducted using the following databases: PubMed, Scopus, Science Direct, and PsycInfo.

Search strategy

Four or more databases will be utilised to obtain the required information. A triple stage approach to searching published literature will be utilised in the development of the search strategy. Firstly, PubMed will be searched for relevant articles. Secondly, the search strategy will be adopted to Scopus, Science Direct, and PsycInfo. Thirdly, the citation list of the selected studies will be further scanned for additional studies. Text words, keywords, and MESH terms such as pharmacological, drugs, medicine, treatment, drug therapy, ASD, autism, autism spectrum disorder, comorbidity, core symptoms, and children will be used in each database. The search terms will be combined using the Boolean operators ‘AND’ and ‘OR’ as indicated in Appendix 2.

Data Selection

This systematic review will be assessed and completed by reviewers (J.M, E.W, S.B.K, and F.O). Studies will be filtered from the year January 2012 – to January 2022. All quantitative studies that involve a medicinal intervention that results in a positive outcome on the core symptom or comorbidity of ASD will be extracted and analysed. Search findings will be conducted independently by 2 authors, J.M and E.W. The selected studies will be exported to Endnote and duplicates will be removed. Studies will then be separated according to 2 thematic descriptions: the treatment of core symptoms or comorbidities of ASD.

Screening of the title/ abstract and full article screening will be done independently by two reviewers for eligibility (J.M and E.W). The rate of the agreement will be calculated. Disagreements will be resolved by the third reviewer (FO). All identified citations will be exported into Endnote and duplicates will be removed.

Data Extraction

A data extraction template (Appendix 1) will be utilised to obtain information that is required for the systematic review. This template is designed to record information related to the name of the author, publication year, country, study design, title, and name of the medication, demographic description, sample size, and main findings. The systematic review will involve the categorisation of data into relevant sections and subsections depending on research done on the pharmacological management of the core symptoms of ASD or the pharmacological management of ASD comorbidities.

Assessment of Methodological Quality.

The Joanna Briggs Critical Appraisal tools (Aromataris et al., 2017) will be utilised to assess the quality of each study. The following tools for quantitative studies will be used; Checklist for Randomized Controlled Trials (Appendix 3). The quality appraisal stage will be done independently by two authors (J.M & E.W). The results obtained from the quality assessment stage will be employed in the final inclusion or exclusion of the study for the systematic review. Disagreements arising will be resolved by the third reviewer (F.O).

Data Synthesis

Extracted data from each study will be evaluated by narrative synthesis for the treatment of core symptoms and ASD-related comorbidities. For narrative synthesis, the quantitative data

will be converted into ‘qualitised data’. This involves transformation into thematic descriptions of the quantitative results from the selected studies in a manner that will answer the review questions. The collected data will be categorised and pooled together based on similarity in meaning to produce a set of integrated results.

Meta-Analysis will be used to analyse the effectiveness of pharmacological treatment options for the core symptoms and comorbidities of ASD. If the studies are heterogeneous in nature and meta-analysis is not possible, the results will be analysed by narrative synthesis only.

Discussion

This protocol will be followed to conduct a systematic review to investigate pharmacological treatment options for the management of the core symptoms and comorbidities of ASD in children and adolescents. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (2020) for systematic reviews will be followed from design to reporting. Joanna Briggs Critical Appraisal tools will be utilised to assess the quality of each study. The pharmacological management of ASD has always represented a challenge of unmet needs. As the number of children diagnosed with ASD increases annually, worldwide, additional effective pharmacological options must become available to improve the quality of life of these individuals. Another area of concern is the lack of approved management options for the core symptoms of ASD. The systematic review would explore treatment options for some of the main ASD comorbidities, and ASD core symptoms in children and adolescents. Additionally, the effectiveness of treatment options for ASD core symptoms will be reported.

Declarations

Author’s contribution statement

All the listed authors contributed significantly to the design, implementation, and development of the manuscript for publication, with approval.

Funding

The authors received no funding to support the review.

Conflicts of interest

The authors declare they have no conflicts of interest.

Ethics Approval

Not required

Data Availability

Most of the data used in this systematic review are publicly available.

Ethical Considerations

Ethical approval will not be required since no individual data will be used. The results will be disseminated for publication in a reputable medical journal.

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2.2 Systematic Review

Pharmacological Management of Core Symptoms and Comorbidities of Autism Spectrum Disorder in Children and Adolescents: A Systematic Review

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The systematic review has also been registered on Open Science Framework (OSF): Registration DOI: https://doi.org/10.17605/OSF.IO/SFZG3.

Abstract

Purpose: The pharmacological management of Autism Spectrum Disorder (ASD) in children remains a challenge due to limited effective management options and the absence of approved drugs to manage the core symptoms. This review aims to describe and highlight effective pharmacological management options employed in managing the core symptoms and comorbidities of ASD from eligible studies over the past decade.

***Methods*:** A search of databases; PubMed, Scopus, Science Direct, and PsycInfo for pharmacotherapeutic options for ASD was conducted in this systematic review. Duplicate studies were removed by utilizing the EndNote citation manager. The studies were subsequently screened independently by two authors. Eligible studies from 01 January 2012 to 01 January 2022 were included based on established eligibility criteria. A narrative synthesis was used for data analysis.

Results: The systematic review provides a comprehensive list of effective management options for ASD comorbidities and core symptoms from 33 included studies. The management options for ASD comorbidities; insomnia, hyperactivity, irritability and aggression, gastrointestinal disturbances, and subclinical epileptiform discharges, were reviewed. Risperidone, aripiprazole, methylphenidate, guanfacine, levetiracetam, and atomoxetine are examples of effective pharmacological drugs against ASD comorbidities. Additionally, this review identified various drugs that improve the core symptoms of ASD and include but are not limited to, bumetanide, buspirone, intranasal oxytocin, intranasal vasopressin, and prednisolone.

Conclusion: This review has successfully summarized the pharmacological advancements made in the past decade to manage ASD. Although there is still no pharmacological cure for ASD core symptoms or additional drugs that have obtained regulatory approval for use in ASD, the availability of promising pharmacological agents are under evaluation and study.

Keywords: pharmacotherapy, therapeutic agent, effectiveness, outcome measure, randomized clinical trial, narrative synthesis

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Introduction

Autism spectrum disorder (ASD) refers to a neurodevelopment disorder that is characterized by difficulties with social communication, social interaction, and restricted and repetitive patterns in behaviors, interests, and activities. By definition, the symptoms are present early on in development and affect daily functioning. The term 'spectrum' is used because of the heterogeneity in the presentation and severity of ASD symptoms [1]. The core symptoms of ASD include persistent deficits in social communication and social interaction across multiple contexts, as manifested by deficits in social-emotional reciprocity, nonverbal communicative behaviors, and developing, maintaining, and understanding relationships. Restricted, repetitive patterns of behavior, interests, or activities are also identified as core symptoms of ASD and manifest as insistence on sameness and inflexible adherence to routines, highly restricted, fixated interests that are abnormal in intensity or focus, hyper or hypo reactivity to sensory input and stereotyped or repetitive motor movements, use of objects, or speech [2]. Most children who present with ASD, also experience a range of medical comorbidities. Common underlying medical conditions include anxiety, depression, epilepsy, gastrointestinal and immune function disorders, metabolic disorders, and sleep disorders [3].

According to a recent systematic review update on the global prevalence of ASD, approximately 1/100 children are diagnosed with ASD around the world [4]. While various medications are undergoing clinical trials for use in relieving ASD symptoms, some of the commonly prescribed medications include second-generation antipsychotics, selective serotonin reuptake inhibitors (SSRIs), stimulants, and alpha-2 adrenergic

agonists [5]. Risperidone and aripiprazole are currently the only medications that the Food and Drug Administration (FDA) has approved for symptoms associated with ASD, targeting the irritability often associated with this medical condition [6]. Medicines for treating the core symptoms of ASD have long represented an area of unmet need since few drugs effectively relieve these symptoms, and none of the options currently used, work well for every individual. The FDA has also yet to approve a medicine for treating ASD core characteristics [7].

Considering the triad of symptoms experienced by individuals with ASD and the increasing number of children diagnosed with the condition, it is apparent that additional therapeutic agents become readily available and accessible. This study aims to systematically review potential options for the pharmacological management of ASD in children and adolescents by identifying successful therapeutic agents against the core symptoms and comorbidities of ASD.

Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (2020) for systematic reviews were followed from design to reporting [8].

Study Objectives

- To develop a comprehensive list of pharmaceutical agents that are in use for the management of the core symptoms of ASD.
- To identify available pharmacological options for the management of ASD-related comorbidities.
- To review and discuss therapeutic outcomes for all included studies.

Study Eligibility

Inclusion Criteria

The PICO framework was used to determine the eligibility of studies for this review;

- P – Population/participants: Children and adolescents (male and female) diagnosed with ASD (Autistic Disorder, Asperger's Syndrome, or Pervasive Development Disorder) and between the ages of 2 and 18 years old.

- I – Intervention: Pharmacological agents for the management of ASD, including vitamins and dietary supplements when used for medicinal purposes to manage the core symptoms and/or the comorbidities of ASD.
- C – Comparison: Placebo, different pharmaceutical agents, or non-pharmacological therapeutic options to which ASD management agents of focus were compared.
- O – Outcome: An outcome measure that resulted in an improvement in the core symptoms of ASD and/or ASD comorbidity.

Exclusion Criteria

- Non-English studies.
- Studies that do not have the outcome of interest.
- Studies before the year 2012 and after 01 January 2022.
- Studies that were not randomized control trials due to the large volume of studies available and the accuracy and reduction of bias in results in this type of study design [9].
- Studies that involved individuals who were not diagnosed with ASD.
- Studies with individuals under the age of 2 and over the age of 18.

Information Sources and Search Strategy

A comprehensive search of 4 databases, PubMed, Scopus, Science Direct, and PsycInfo, was conducted by J.M and E.W. A triple stage approach to searching published literature was utilized in the development of the search strategy. Firstly, PubMed was searched for relevant articles. Secondly, the search strategy was adopted to Scopus, Science Direct, and PsycInfo. Thirdly, the citation list of the selected studies was further scanned for additional studies. Text words, keywords, and MESH terms such as pharmacological, drugs, medicine, treatment, drug therapy, ASD, autism, autism spectrum disorder, comorbidity, core symptoms, and children were used in each database. The search terms were combined using the Boolean operators 'AND' and 'OR' as indicated in Appendix 2.

Screening and Selection of Studies

Titles and Abstract Screening

Four databases, PubMed, Scopus, Science Direct, and PsycInfo were searched independently by two authors (J.M & E.W) according to the search strategy designed. The duplicate results and those studies with titles and abstracts that did not meet eligibility criteria were removed. There were no disagreements between J.M and E.W.

Full-text Screening

After the removal of duplicates and results with irrelevant titles and abstracts, the remaining studies went through full-text screening. This step was also done independently by two authors (J.M & E.W). Additional articles that did not meet the inclusion criteria due to ineligible study design, study population, and target age group, were removed. Review articles and studies without the desired outcome of interest were also removed. The remaining studies were selected for final inclusion in the review. There were no disagreements between J.M and E.W.

Quality Assessment

The Joanna Briggs Critical Appraisal tool, Checklist for Randomized Controlled Trials [10] was utilized to assess the quality of each study. This appraisal tool contained questions related to true randomization, concealment of allocation to treatment groups, blinding at all stages, the use of reliable outcome measures, and the performance of appropriate statistical analysis. The quality appraisal stage was done independently by two authors (J.M & E.W). The articles were then scored based on their quality scores and classified as less than 50% (low-quality studies), 50% to 75% (moderate-quality studies), or greater than 75% (high-quality studies). There were no disagreements between J.M and E.W.

Data Extraction

A data extraction tool (Appendix 1) was utilized to obtain the data required for this systematic review. The tool was designed by J.M to record data related to the therapeutic agent, study reference, sample size, and country. For ASD comorbidities, the name of the comorbidity and treatment effectiveness from the study were recorded. For ASD core symptoms, the improved outcome measure and treatment effectiveness were recorded. There was a greater emphasis on improved outcome measures and treatment effectiveness for ASD core symptoms due to the absence of a cure and no approved pharmacological treatments [11].

Data Synthesis

Extracted data from the studies were analyzed through a narrative synthesis for the management options of core symptoms and ASD-related comorbidities. For narrative synthesis, the quantitative data was converted into 'qualitised data'. This involved the transformation into thematic descriptions of the quantitative results from the selected studies in a manner that would answer the review questions. The collected data were categorized and pooled together based on similarity in meaning to produce a set of integrated results. It was not possible to perform a meta-analysis on the effectiveness of management options since the studies had different outcome measures and different drugs therefore an overall quantitative estimate could not be performed [12].

Results

Search Results

The data collection process began in February 2022 by J.M and E.W. Based on the search of 4 databases there were a total of 1655 citations (PubMed = 71, Science Direct = 854, Scopus = 522, PsycInfo = 208; Figure 1). Upon removal of duplicate results, the articles were reduced to 904. These articles were screened by title and abstract according to eligibility criteria and a further 819 results were removed. A total of 84 articles were then subjected to full-text assessment. A further 51 studies were excluded for reasons indicated in the PRISMA flow diagram (Figure 1); 33 studies were included in the systematic review. There were no disagreements between J.M and E.W.

Quality Assessment

The 33 selected studies were appraised for quality by utilizing the Johanna Briggs Institute (JBI) critical appraisal checklist for randomized control trials. Appraisal of individual studies using the JBI appraisal method is shown as supplementary information (Appendix 3). The majority of the studies (52%) were of the highest quality scoring (100%) and 48% of studies were of a high-quality (score > 75%). None of the studies were eliminated based on methodological quality evaluation outcomes as the authors wanted to compile a comprehensive list of all potentially effective therapeutic agents. There were no disagreements between J.M and E.W.

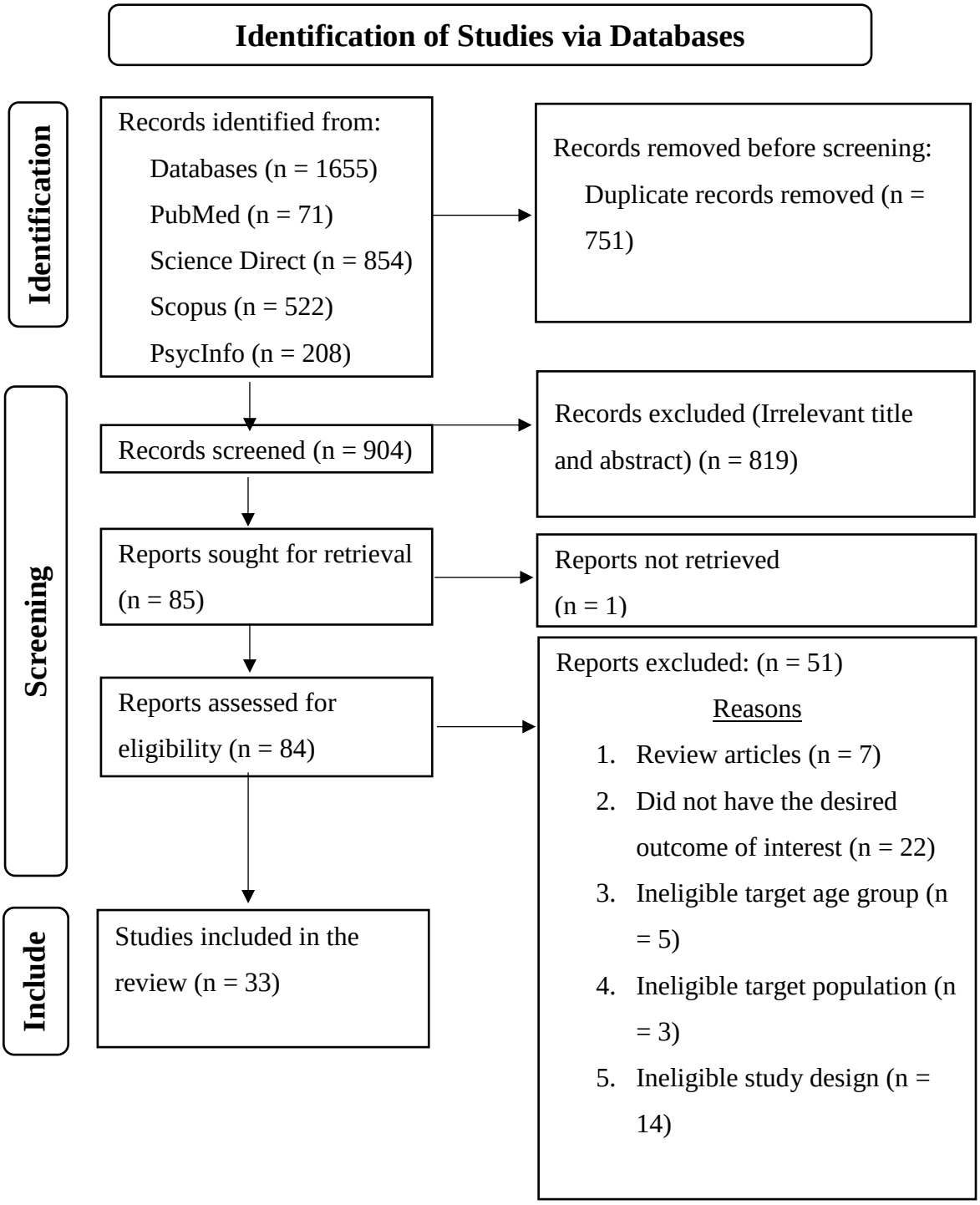

Figure 1: Summary of Study Selection Procedure

Study Characteristics

The data extracted from the 33 studies are detailed in Table 1: Summary of Study Characteristics and Management Effectiveness of ASD Comorbidities, and Table 2: Summary of Study Characteristics and Management Effectiveness of ASD Core

Symptoms. The articles selected were published from the year 2012 up to and including the year 2021. This produced a set of results that describe current trends in the pharmacological management of ASD over the past decade. The study design of all selected articles included in this review was randomized control trials. The sample size of participants across all studies ranged from 13 to 166 participants.

Demographic and Participant's Characteristics

Of the selected studies, 52% (n = 17) were conducted in the USA and 18% (n = 6) were conducted in Iran. The rest of the studies were conducted in New Zealand (n = 2), Asia (n = 4), France (n = 2), Australia (n = 1) and Brazil (n = 1). Interestingly, there were no studies conducted in Africa. The main objective of all studies was to examine the effect of a pharmacological intervention compared to a placebo when used to manage an ASD comorbidity or core symptom. All studies included male and/or female children and/or adolescents diagnosed with ASD. The population age group for the included studies ranged between 2 and 18 years

Review Findings

Management Options for ASD Comorbidities

Table 1: Characteristics of Studies for the Treatment of ASD Comorbidities.

Therapeutic Agent	Sample Size	Country	Comorbidity	Results and Treatment Effectiveness
Aripiprazole [27]	92	Japan	Irritability	At week 8, the least square mean decrease from baseline in the parent/caregiver-rated Aberrant Behavior Checklist (ABC) Japanese Version - irritability subscale score was significantly greater for patients who received aripiprazole, (probability [p] = 0.044). By week 8, the aripiprazole group also showed a statistically

				significant improvement in clinician-rated Clinical Global Impression (CGI) -Improvement scores when compared to the placebo group ($p = 0.003$).
Atomoxetine [21]	128	United States	Hyperactivity	Primary outcome measures were the parent-rated hyperactivity symptoms on the Swanson, Nolan, and Pelham (SNAP) scale. On the SNAP, Atomoxetine (ATX), ATX plus Parent Therapy (PT), and placebo plus PT were each superior to placebo (p values of 0.0005, 0.0004, and 0.025, respectively). For noncompliance symptoms, ATX and ATX plus PT were superior to placebo (p values 0.03 and 0.0028, respectively).
Guanfacine [17]	62	United States	Hyperactivity	The guanfacine group showed a 43.6% decline in scores on the ABC - hyperactivity subscale compared with a 13.2% decrease in the placebo group. The rate of positive response (much improved or very much improved on the CGI - Improvement scale) was 50% (15 of 30) for guanfacine compared with 9.4% (3 of 32) for placebo.
Guanfacine [30]	62	United States	Oppositional behavior	After 8 weeks of treatment, parent ratings of oppositional behavior on the Home Situation Questionnaire-Modified for ASD declined by

				44% (per item mean from 3.4 to 1.9) in the guanfacine group compared to 12% (from 3.3 to 2.9) for placebo (p = 0.004).
L-Carnosine [16]	43	Iran	Sleep disturbances	L-Carnosine supplementation significantly reduced sleep duration (p = 0.04), parasomnias (p = 0.02) and total sleep disorders score by 7.59% (p = 0.006) when compared with the control group.
Levetiracetam [31]	70	China	Subclinical epileptiform discharges (SEDs)	Before the treatment, SEDs were identified in each patient. At the 6-month follow-up, SEDs were absent in 24 of the 32 patients (75.0%) in the treatment group and 5 of the 35 patients (14.3%) in the control group.
Melatonin [14]	125	United States	Insomnia	After 13 weeks of double-blind treatment, participants slept on average 57.5 minutes longer at night with melatonin compared to 9.14 minutes with placebo (adjusted mean treatment difference -32.43 minutes; p = 0.034). Sleep latency decreased by 39.6 minutes on average with melatonin and 12.5 minutes with placebo (adjusted mean treatment difference -25.30 minutes; p = 0.011) without causing an earlier wakeup time.

Memantine as adjunctive treatment to risperidone [24]	40	Iran	Irritability, stereotypic behavior, and hyperactivity.	The difference between the two treatment arms was significant as the group that received memantine had a greater reduction in ABC-Community subscale scores for irritability ($p < 0.001$), stereotypic behavior ($p < 0.01$), and hyperactivity ($p < 0.01$).
Methylphenidate [18]	60	United States	Hyperactivity	On the primary outcome measure (ABC hyperactivity - subscale), the medium and high-dose levels of methylphenidate were superior to placebo. On the mean Parent Target Problem (PTP) rating, only the high dose was superior to the placebo. The main effects of the mixed-effects linear model across the four doses were $p = 0.06$ for the PTP scores and $p = 0.0001$ for the ABC-hyperactivity subscale.
Methylphenidate [20]	24	United States	Hyperactivity	Children with ASD and ADHD symptoms made significantly fewer omission errors, ($p < 0.001$), and commission errors ($p = 0.005$) on methylphenidate, relative to placebo. Similarly, improvements were also noted for impulsivity/disinhibition and selective attention for visual and auditory processing.
Methylphenidate [19]	24	United States	Hyperactivity	Methylphenidate treatment was associated with consistent

				improvements in parent ratings in core symptoms of ADHD, as well as in symptoms closely associated with ADHD. Significant dose-related improvements in attention were noted on the Conner's ($p < 0.001$) and the SNAP-IV ($p = 0.001$). Significant effects of methylphenidate treatment on CGI of both current severity and improvement were found by both the psychiatrist and psychologist.
N-acetylcysteine (NAC) [29]	33	United States	Irritability	Follow-up data were available on 14 subjects in the NAC group and 15 in the placebo group. Oral NAC was well tolerated with limited side effects. Compared with placebo, NAC resulted in significant improvements on the ABC-irritability subscale ($p < 0.001$).
NAC as adjunctive treatment to Risperidone [28]	40	Iran	Irritability	The mean score of irritability in the NAC plus risperidone and placebo plus risperidone groups at baseline were 13.2(5.3) and 16.7(7.8), respectively. The scores after 8 weeks were 9.7(4.1) and 15.1(7.8), respectively. Repeated measures showed that there was a significant difference between the two groups after 8 weeks baseline.

Palmitoylethano-lamide (PEA) as adjunctive to Risperidone [23]	70	Iran	Irritability and Hyperactivity/ Noncompliance symptoms	At the trial endpoint (week 10), a combination of PEA and risperidone had superior efficacy in ameliorating irritability and hyperactivity/noncompliance symptoms ($p = 0.001$) compared with a risperidone plus placebo regimen.
Probiotics [25]	80	Taiwan	Opposition/ Defiance behaviors and Hyperactivity.	The scores of The Swanson, Nolan, and Pelham-IV-Taiwan version (SNAP-IV) were similar between the probiotic and placebo groups both on baseline and week 4. Exploratory analyses displayed reduced total scores ($p = 0.01$), hyperactivity and impulsivity ($p = 0.04$), and opposition and defiance ($p = 0.045$) over four weeks in the probiotic group. The placebo group did not exhibit these changes.
Probiotics [32]	13	United States	Gastrointestinal (GI) complaints	A parent-selected target symptom showed significant improvement in GI complaints on probiotics compared with placebo ($p = 0.02$). Probiotic effects carried over through the 3-week washout.
Risperidone or Aripiprazole [26]	80	United States	Irritability	All patients significantly improved on the ABC-irritability subscale after 1 week and continued for the remaining 9 weeks and the extension phase. Improvement was

				greatest in the risperidone group at every assessment period and was statistically significantly better than that in the aripiprazole group at weeks 3 and 6 ($p < 0.05$).
Vitamin D and Omega-3 long-chain polyunsaturated fatty acids [22]	111	New-Zealand	Irritability and Hyperactivity	After 12 months, children receiving omega-3 fatty acids ($p = 0.001$) and vitamin D ($p = 0.01$) had greater reduction in irritability than placebo. Compared to placebo, children on vitamin D also had a greater reduction in hyperactivity ($p = 0.047$).

Notes – A p value < 0.050 was considered statistically significant for studies included in Table 1.

Insomnia and Sleep Disturbances

Melatonin - Melatonin is a hormone produced in response to darkness that assists with the timing of circadian rhythms (24-hour internal clock) and with sleep [13]. According to a randomized control trial [14], melatonin illustrated improved sleep duration and onset when compared to placebo.

L- Carnosine - Carnosine, a substance produced naturally by the body is classified as a dipeptide, a compound made up of two linked amino acids and is highly concentrated in muscle tissue and the brain [15]. A randomized control trial [16] indicated that carnosine supplementation in ASD individuals (4 – 16 years old) could be effective in improving sleep disturbances, in particular, sleep duration and parasomnias subscales when compared to placebo.

Hyperactivity

Guanfacine - In a multisite, randomized clinical trial, extended-release guanfacine was compared with placebo in children with ASD. The guanfacine group displayed a

significant decline in scores on the Aberrant Behavior Checklist (ABC)-hyperactivity subscale when compared to the placebo group. Results indicated that extended-release guanfacine was safe and effective for reducing hyperactivity, impulsiveness, and distractibility in children with ASD [17].

Methylphenidate - Three randomized control trials displayed the effectiveness of methylphenidate for the treatment of hyperactivity. A multisite, 4-week, randomized crossover trial compared three dose levels (low, medium, and high) of methylphenidate with placebo. On the primary outcome measure, the ABC-hyperactivity subscale, the medium and high-dose levels were superior to placebo [18]. Similar results were seen in a second study where methylphenidate treatment was associated with significant declines in hyperactive and impulsive behavior at both home and school [19]. Additionally, a within-subject, crossover, placebo-controlled design study revealed that methylphenidate treatment was associated with significant performance gains on cognitive tasks tapping sustained attention, selective attention, and impulsivity/inhibition in children with ASD [20].

Atomoxetine - In a double-blind trial of atomoxetine (ATX) and parent therapy (PT), 128 children (ages 5-14 years) with ASD and Attention Deficit Hyperactivity Disorder (ADHD) symptoms were randomized to ATX, ATX plus PT, placebo plus PT, or placebo. Primary outcome measures indicated that both ATX and PT resulted in significant improvement in ADHD symptoms, whereas ATX (both alone and combined with PT) was associated with significant decreases in measures of noncompliance. The study concluded that subsequent research should include a comparison of atomoxetine with other psychopharmacological treatments for ADHD along with the impact of psychosocial interventions [21].

Additionally, vitamin D [22], Palmitoylethanolamide (PEA) as adjunctive to risperidone [23], memantine as adjunctive to risperidone [24], and probiotics [25] also displayed effectiveness in reducing hyperactivity compared to placebo.

Irritability, Aggression, Aberrant behavior, Anxiety, and Maladaptive Behaviors.

Aripiprazole and Risperidone - Both these agents have FDA approval for the aggression and irritability seen in children with ASD. A randomized double-blind parallel-group

study of risperidone or aripiprazole was conducted in three academic medical centers and a single private pediatric practice. Pharmacotherapy (treatment with risperidone or aripiprazole) of patients with ASD resulted in behavioral improvement within 1 week and lasted at least 22 weeks. A trend was observed for greater improvement in the risperidone group at all assessment points, but the difference compared to aripiprazole reached statistical significance only at weeks 3 and 6. This trial supports previous results of drug effectiveness and safety in patients with ASD from other trials and extends the evidence-based support for choosing an FDA-approved drug for initial pharmacotherapy for ASD [26].

Aripiprazole - A randomized, double-blind, placebo-controlled 8-week study in Japan evaluated the effectiveness and safety of aripiprazole in the treatment of irritability in children and adolescents (6-17 years) with ASD. Aripiprazole produced a significant improvement in the mean parent/caregiver-rated ABC Japanese Version-irritability subscale score relative to placebo. Aripiprazole displayed effectiveness, safety, and tolerability in the treatment of irritability associated with ASD in Japanese children and adolescents [27].

PEA, N-Acetylcysteine (NAC), or Memantine as Adjunctive Treatment to Risperidone - Three studies conducted in Iran investigated the addition of PEA, NAC, or memantine to risperidone for enhanced therapeutic effect when treating irritability and other aberrant behaviors seen in ASD. A randomized, parallel-group, double-blind placebo-controlled trial was conducted to investigate the effectiveness of co-management with risperidone and PEA in children with ASD. At the trial endpoint (week 10), the combination of PEA and risperidone had superior effectiveness in ameliorating the irritability and hyperactivity/noncompliance symptoms compared with a risperidone plus placebo regimen [23]. Similar results were seen with NAC as adjunctive management for ASD as risperidone plus NAC decreased irritability more than risperidone plus placebo in children and adolescents with ASD [28]. Additionally, a study utilizing risperidone and memantine illustrated differences between the two management arms as the group that received memantine had a greater reduction in irritability, stereotypic behavior, and hyperactivity [24].

NAC - A study of NAC as monotherapy also produced effective results as NAC resulted in significant improvements on the ABC-irritability subscale compared with placebo [29].

Additionally, other randomized controlled trials included in this review that utilize vitamin D and omega-3 long-chain polyunsaturated fatty acids [22], probiotics [25], guanfacine [30], and levetiracetam [31] also demonstrated significant improvements in irritability, maladaptive or oppositional behaviors seen in children and adolescents with ASD.

Gastrointestinal Disturbances

Probiotics – This therapeutic agent was effective against common gastrointestinal (GI) symptoms seen in children with ASD. In a study conducted in the United States, thirteen children, 3 - 12 years of age with ASD and GI symptoms were randomized into a probiotic crossover trial of 8 weeks each on VISBIOME (a probiotic that contains eight probiotic species, mostly Lactobacillus and Bifidobacterium) and placebo separated by a 3-week washout. A parent-selected target symptom showed significant improvement in GI complaints on probiotics compared with placebo. The probiotic formulation was safe and suggested a health benefit in children with ASD and GI symptoms who retained lactobacillus [32]. Additionally, two open-label studies [33,34], not included in this review due to the study design, also supported the improvement of gastrointestinal comorbidities attributed to the use of probiotics in children with ASD.

Subclinical Epileptiform Discharges (SEDs)

Levetiracetam - SEDs are common in pediatric patients with ASD. A physician-blinded, randomized controlled trial investigated an association between the anticonvulsant drug levetiracetam and SEDs in children with ASD. Levetiracetam was effective for controlling SEDs in pediatric patients with ASD and was also associated with improved behavioral and cognitive functions. The rate of electroencephalographic normalization was also significantly higher in the treatment group [31].

Management Options for ASD Core Symptoms

Therapeutic Agents for Restricted and Repetitive Behaviors or Interests

Bumetanide - Although a study conducted in the Netherlands for bumetanide displayed no superior effectiveness for the trial's primary outcome measures, it did result in an improvement on a secondary outcome measure; The Repetitive Behavior Scale-Revised (RBS-R), and the observed effect was more explicit in female participants [35].

Buspirone - A study involving the use of buspirone concluded that buspirone treatment may be considered for further exploration as a useful adjunct therapy to target restrictive and repetitive behavior in conjunction with early behavioral intervention, to provide therapeutic coverage for the full range of ASD core features and adaptive skills in young children with ASD [36].

Fluoxetine - In a multicenter, randomized, placebo-controlled clinical trial, participants aged 7.5-18 years with ASD and a total score of 6 or higher on the Children's Yale-Brown Obsessive Compulsive Scale, modified for pervasive developmental disorder (CYBOCS-PDD) were recruited from 3 tertiary health centers across Australia. Treatment with fluoxetine compared with placebo resulted in significantly lower scores for obsessive-compulsive behaviors at 16 weeks [37].

Guanfacine - Repetitive behavior showed a significantly greater decline in guanfacine-managed participants compared to placebo. Results from this study concluded that guanfacine can be considered a first-line treatment for children with ASD who exhibit hyperactivity, as well as oppositional behavior, or repetitive behavior. Future studies could focus on repetitive behavior or anxiety, symptoms with limited treatment options [30].

Omega-3 fatty acids - Stereotype behaviors significantly improved by intervention with omega-3 fatty acids according to the Gilliam Autism Rating Scale – second edition (GARS-2) [38].

Therapeutic Agents for Social Communication and Social Interaction Challenges

Table 2: Summary of Study Characteristics and Management Effectiveness of ASD Core Symptoms.

Therapeutic Agent and Study Reference	Sample Size	Country	Improved Outcome Measure	Results and Management Effectiveness
Atomoxetine as adjunctive treatment to Risperidone [39]	44	Iran	Childhood Autism Rating Scale (CARS), and the Clinical Global Impressions (CGI)	Atomoxetine compared to placebo showed significant improvement in global impression and severity index in CGI, and also in the total score of CARS and 7 subscales of CARS (probability [p] = 0.05).
Bumetanide [41]	88	France	CARS, the Social Responsive Scale (SRS), and the CGI-Improvement scale (CGI-I)	23 treated children had more than a six-point improvement in the CARS compared with only one placebo-treated individual. Bumetanide significantly improved CGI (p = 0.0043) and the SRS score by more than 10 points (p = 0.02)
Bumetanide [35]	92	Netherlands	Repetitive Behavior Scale−Revised (RBS-R)	A superior effect was found on one of the secondary outcomes, RBS-R (mean difference -4.16, 95% Confidence Interval [CI] = -8.06 to -0.25 in placebo, p = 0.0375)

Bumetanide [40]	66	France	CARS, CGI-I, and The Autism Diagnostic Observation Schedule (ADOS)	After 90 days of bumetanide, the treated groups shifted from severe (CARS >36.5) to mild or medium severity (< 36.5). The total CARS score decreased on average by 5,6 points in the bumetanide group compared to 1,4 points in the placebo group, p = 0,0044. In CGI-I, 77.7% of children had small or significant amelioration in bumetanide compared with only 33.3% in placebo. Average gains of ADOS total scores increased moderately for treated (mean = 7.8, Standard Deviation [SD] = 7.4) versus placebo (mean = 5.3, SD = 6.6).
Bumetanide [42]	119	China	CARS	The total CARS score decreased on average by 2.23 (SD: 1.29) points in the bumetanide group and 1.28 (SD: 0.91) points in the placebo group.
Buspirone [36]	166	United States	ADOS	The ADOS and Repetitive Behavior score showed a time by treatment effect (p = 0.006), the 2, 5 mg buspirone group showed significant improvement (p = 0.003) while placebo and 5 mg buspirone groups showed no change.

Fluoxetine [37]	146	United States	Children's Yale-Brown Obsessive-Compulsive Scale-Modified for Pervasive Developmental Disorder (CYBOCS-PDD)	The mean CYBOCS-PDD score from baseline to 16 weeks decreased in the fluoxetine group from 12.80 to 9.02 points (3.72-point decrease; 95% CI, -4.85 to -2.60) and in the placebo group from 13.13 to 10.89 points (2.53-point decrease; 95% CI, -3.86 to -1.19)
Folinic acid [43]	48	United States	Vineland Adaptive Behavior Scale, The Autism Symptom Questionnaire, and The Behavioral Assessment System	Improvement in verbal communication was significantly greater in participants receiving folinic acid as compared with those receiving placebo, resulting in an effect of 5.7 standardized points with a medium-to-large effect size (Cohen's d = 0.70).
Guanfacine [30]	62	United States	Children's Yale-Brown Obsessive-Compulsive Scale-Modified for ASD (CYBOCS-ASD)	Repetitive behavior on the CYBOCS-ASD showed a significantly greater decline in guanfacine treated participants compared to placebo (24% verse < 1%)

Intranasal Oxytocin [44]	32	United States	SRS	Oxytocin-treated individuals showed greater improvement in social abilities (as measured by the SRS Total Raw Score) than placebo-treated individuals following completion of the 4-week trial (p = 0.0275). Importantly no oxytocin-treated individual's social abilities worsened, compared to 6/16 (37.5%) of placebo-treated individuals that did.
Intranasal Oxytocin [45]	31	Australia	SRS	Oxytocin resulted in a significant mean improvement in the SRS (109.1 vs 98.5, $p < 0.001$). A difference-in-difference approach found that participants achieved a significantly greater mean improvement on the SRS at post-test (as compared with pre-test) when administered oxytocin verse placebo. Experimenter-rated impressions of clinical global improvement were also significantly greater for oxytocin (72%, 21/29) compared with placebo (41%, 12/29, $p < 0.05$).
Intranasal vasopressin (AVP) [46]	30	United States	SRS, CGI-I, Reading the Mind in the Eyes Test (RMET) and	Individuals with ASD, treated with intranasal AVP for 4 weeks showed greater improvement when compared to placebo in their social abilities as assessed

			Facial Emotion Recognition Test (FERT)	by 4 different outcome measures; the SRS-2 score (p = 0.0052), the CGI-I scale (p = 0.0145), the RMET (p = 0.047); and the FERT (p = 0.0132).
Prednisolone [47]	38	Brazil	Language Development Assessment (ADL) and the Child Language Test in Phonology, Vocabulary, Fluency, and Pragmatics (ABFW).	Prednisolone increased the global ADL score in children younger than 5 years of age who had developmental regression (p = 0.0057). The ABFW's total of communicative acts also responded favorably to those participants with regression (p = 0.054).
Omega-3 fatty acids [38]	54	Iran	The Gilliam Autism Rating Scale-second edition (GARS-2).	The intervention group had significantly improved stereotyped behaviors (p = 0.002), social communication (p = 0.02) and the GARS-2 score (p = 0.001).
Methyl B12 [48]	57	United States	CGI-I score	The CGI-I score was statistically significantly better (lower) in the methyl B12 group (2, 4) than in the placebo group (3, 1) displaying a 0, 7 greater improvement in the methyl B12 group, p = 0.0005.
Vitamin D and Omega-3 long-chain	73	New Zealand	SRS	When all children were included in the analysis, two outcome comparisons (treatments vs.

polyunsaturated fatty acids [49]	placebo) showed greater improvements: Omega fatty acids (OM) and OM and Vitamin D (VID) combination (VIDOM) (p = 0.01) for SRS-awareness. When only children with elevated interleukin-1β were included, five outcomes showed greater improvements: OM (p = 0.01) for SRS-total; OM (p = 0.03) for SRS-social communicative functioning; VID (p = 0.01), OM (p = 0.003), and VIDOM (p = 0.01) for SRS-awareness.

Notes – A p value < 0.050 was considered statistically significant for studies included in Table 2.

Atomoxetine as Adjunctive Treatment to Risperidone - A study done in Iran illustrated that the addition of atomoxetine to risperidone displayed improvements for 7 subscales on the Childhood Autism Rating Scale (CARS) which included relationship to people, emotional response, body use, listening response, fear and nervousness, nonverbal communication, and activity level. The study concluded that the addition of atomoxetine to risperidone resulted in significant improvements compared to placebo and risperidone [39].

Bumetanide – A study conducted in France that examined the effects of bumetanide on the core symptoms of ASD indicated that bumetanide reduced significantly the CARS, Clinical Global Impressions (CGI), and The Autism Diagnostic Observation Schedule (ADOS) values when the most severe cases were removed. Several qualitative comments from the parents of children in the study attested to bumetanide's positive effects, including a greater presence of the child, facilitated visual communication, and social exchanges. Results suggested a promising novel therapeutic approach to treating ASD

children [40]. An additional study conducted in France suggested that bumetanide was effective in improving ASD-related symptoms across the pediatric age range as assessed by CARS, the CGI-Improvement scale (CGI-I), and the Social Responsive Scale (SRS). Interestingly, responders were found in all subpopulations, ages, and ASD severity according to CARS scores suggesting that the treatment was not restricted to a particular group [41]. Thirdly, a randomized, double-blind, placebo-controlled trial of bumetanide in a large group of children with ASD, aged 3−6 years, found that bumetanide at a dose of 0.5 mg twice daily significantly improved the core symptoms of ASD as measured by the primary clinical outcome (CARS total score). It was concluded that bumetanide is safe and effective in improving disease severity, attenuating social impairment, and improving the activity level of children with ASD, and therefore provides a viable alternative therapeutic option for young patients in addition to behavioral interventions [42].

Folinic acid - Improvement in verbal communication was significantly greater in participants receiving folinic acid as compared with those receiving placebo according to three different subscales: Vineland Adaptive Behavior Scale, The Autism Symptom Questionnaire, and The Behavioral Assessment System. Folate receptor-α autoantibody (FRAA) status was predictive of response to treatment. For FRAA-positive participants, improvement in verbal communication was significantly greater in those receiving folinic acid as compared with those receiving placebo, indicating that folinic acid treatment may be more efficacious in children with ASD who are FRAA positive [43].

Intranasal Oxytocin - Two studies included in the review demonstrated the effectiveness of intranasal oxytocin on social communication and social interaction challenges. In the study conducted in the United States, the efficacy and tolerability of intranasal oxytocin treatment (24 International Units, twice daily) were tested in 32 children with ASD, aged 6-12 years old. When pretreatment neuropeptide measures were included in the statistical model, oxytocin compared with placebo treatment significantly enhanced social abilities in children with ASD. Importantly, pretreatment blood oxytocin concentrations also predicted treatment response, such that individuals with the lowest pretreatment oxytocin concentrations showed the greatest social improvement [44]. Additionally, a study in Australia also resulted in a significant mean improvement on the SRS parent report when oxytocin was compared to placebo. The study was the first clinical trial to support the

potential of oxytocin as an early intervention for young children with ASD to help improve social interaction deficits [45].

Intranasal Vasopressin (AVP) - A study conducted in the USA indicated that individuals managed with intranasal AVP for 4 weeks showed greater improvement in their social abilities as assessed by the primary outcome measure, the Social Responsive Scale-2 (SRS-2). AVP-managed individuals also showed greater clinician-evaluated improvement in social communication abilities as assessed by the CGI-I scale. Similarly, child participants managed with intranasal AVP versus placebo showed enhanced theory of mind abilities, as assessed by the Reading the Mind in the Eyes Test (RMET), and increased facial emotion recognition abilities as assessed by the Facial Emotion Recognition Test (FERT) [46].

Prednisolone - A study conducted in Brazil that aimed to describe the effect of prednisolone on the language of children with ASD resulted in positive therapeutic outcomes as indicated by the Language Development Assessment (ADL) and the Child Language Test in Phonology, Vocabulary, Fluency, and Pragmatics (ABFW). The benefit of prednisolone for language scores was more evident in participants who were younger than five years, with a history of developmental regression. The prednisolone dose of 1 mg/kg/day used during the first eight weeks of the trial was low therefore the study concluded that a higher dose would have achieved more favorable intervention outcomes [47].

Additionally, studies that utilize non-pharmacological agents; methyl B12 [48] and vitamin D and omega-3 long-chain polyunsaturated fatty acids [49] also displayed effectiveness for social communication and social interaction challenges as indicated numerically in table 2.

Discussion

This review highlights and describes the effectiveness of various therapeutic agents for ASD comorbidities and core symptoms through thirty-three randomized control trial studies conducted over the past decade. As indicated above, a meta-analysis to perform a quantitative estimate of drug effectiveness was not possible due to the heterogeneous nature of the selected studies [12]. Various trends could be observed from the included

studies in this review. Firstly, the addition of therapeutic agents to risperidone improved the effectiveness in the management of ASD comorbidities as seen in the following studies [23,24,28]. A similar observation was found with atomoxetine as adjunctive treatment to risperidone and produced improved results on the core symptoms compared to placebo and risperidone [39]. All four of these studies were conducted in Iran and therefore it would be interesting to observe results from similar studies conducted elsewhere internationally. Bumetanide was the agent of choice for improvement in the core symptoms of ASD since it produced effective results in four different randomized control trials [35,40-42]. The results also indicated that bumetanide improved both core symptoms (restricted and repetitive behaviors or interests and social communication and social interaction challenges). The geographical distribution of the studies with bumetanide also spanned across three different countries: France [40,41], Netherlands [35], and China [42]. Intranasal dosage preparations observed in the form of oxytocin [44,45] and vasopressin [46] produced effective results for social communication and social interaction challenges. Intranasal vasopressin as a pharmacological treatment option produced positive results on the core symptoms according to four improved outcome measures from a single study [46]. Future studies involving intranasal vasopressin should be conducted by utilizing the same target population and greater sample size to determine if the same replication of results is observed. A study involving the use of prednisolone displayed promising effectiveness against social communication deficits and this was the first prospective study in medical literature based on a double-blinded, randomized, placebo-controlled clinical trial on the treatment of ASD with corticosteroids [47]. Two pharmacological agents, atomoxetine and guanfacine which are both indicated for use in ADHD, resulted in positive outcomes on the core symptoms and comorbidities of ASD. Guanfacine in some studies resulted in improvements in hyperactivity [17], oppositional behavior [30], and core symptoms [30]. Similarly, studies involving the use of atomoxetine resulted in improvements in hyperactivity [21] and core symptoms [39]. A study in Japan involving the use of aripiprazole produced results that were in line with FDA approval of this pharmacological agent for the management of irritability and aggression seen in ASD individuals [27]. Methylphenidate produced effective results from three different clinical trials for the management of hyperactivity in ASD [18-20]. Epilepsy is a common comorbidity experienced by children with ASD. However, the only antiepileptic drug that appeared in

this review was levetiracetam for the effective management of subclinical epileptiform discharges [31]. Non-pharmacological agents in the form of dietary and vitamin supplements produced effective results for the management of ASD comorbidities and/or core symptoms. According to this review, there were no pharmacological agents available for the management of insomnia and gastric symptoms. However, dietary supplements in the form of melatonin [14] and L-carnosine [16] were effective in the management of insomnia while probiotics produced effective results for gastrointestinal complications [32]. Omega-3 fatty acids displayed effectiveness in irritability [22], repetitive behavior [38], and social communication and social interaction challenges [49]. Additionally, folinic acid [43], vitamin D [49], and methyl B12 [48] produced effective results for the core symptoms of ASD. An important observation, based on this review and the inclusion criteria, is the complete absence of any randomized control trials from South Africa or Africa as a continent. This is an area of concern considering the prediction that 40% of the world's children will live on the continent of Africa by the year 2050 and 1–2% of them are likely to have ASD [50]. Previous international systematic reviews regarding the pharmacological management of ASD in children either involved an investigation of pharmacological interventions for the core symptoms of ASD only example [51,52] or involved a systematic review of psychotropic drug use for ASD comorbidities [53]. Additional systematic reviews included pharmacological management options for severe irritability [54] and ADHD [55] in individuals diagnosed with ASD. To our knowledge, this systematic review could be the only or possibly one of the limited studies that describe effective management options for both ASD core symptoms and comorbidities in children and adolescents over the past ten years.

Limitations

The review was limited to full-text studies from four databases. Also, due to the large volume of studies available on the pharmacological management of ASD, the eligibility criteria for study design were limited to randomized control trials since randomization reduces bias and provides a rigorous tool to examine cause-effect relationships between an intervention and outcome [9]. This indicates the availability of the same or additional therapeutic agents from this review that display effectiveness through open-label trials, case reports, case studies, and other types of study designs. Data analysis was limited to

narrative synthesis due to the heterogeneous nature of the studies retrieved. However, a meta-analysis in the future should not be ruled out if additional studies are conducted for individual drug effectiveness. To ensure results were current trends in the pharmacological management of ASD, eligible studies were selected from 01 January 2012 to 01 January 2022 only.

Conclusion

Since the FDA approval of risperidone and aripiprazole [6], there are still no additional pharmacological agents that have gained a similar therapeutic status for the treatment of ASD core symptoms or comorbidities. However, based on the results of this review, it can be concluded that various drugs are available and it is apparent that sufficient progress has been made over the past decade related to effective management options for ASD core symptoms and comorbidities. Although none of the therapeutic agents included in this review provided a complete resolution or cure of ASD core symptoms, they did display positive outcomes and improved management effectiveness compared to placebo. In the future, based on results from additional effective studies conducted internationally, there is a possibility that certain drugs especially bumetanide and possibly other therapeutic agents included in this review, would be in a position to obtain regulatory approval for use in ASD.

Disclosures

Author's Contribution Statement

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work

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Conflicts of Interest

The authors declare they have no conflicts of interest.

Ethics Approval

Not required

Data Availability

Most of the data used in this systematic review are publicly available.

Ethical Considerations

Ethical approval was not required since no individual data was used. The results will be disseminated for publication in a reputable medical journal.

Chapter Summary

This chapter includes a systematic review on the pharmacological management of ASD core symptoms and comorbidities based on effective international randomized control trials. The following chapter discusses the results of the retrospective study based on the pharmacological management of ASD in children at a public hospital facility in KwaZulu-Natal.

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Chapter 3: Manuscript II

Introduction

The pharmacological management of children diagnosed with ASD at a public hospital in South Africa is discussed in this chapter. This includes prescribing trends for the core symptoms and comorbidities related to ASD as well as therapeutic outcomes. The results also facilitated a comparison of the pharmacological management of ASD in KwaZulu-Natal with various international trends. The chapter is presented in manuscript format in accordance with the College of Health Sciences guidelines for dissertation submission at the University of KwaZulu-Natal (UKZN). The manuscript has been submitted for publication to the Journal: Child Psychiatry and Human Development (Annexure 6) and is still under editorial review. This chapter has been written, formatted, cited, and referenced according to the journal's submission guidelines. The author guidelines for the chosen journal can be viewed in Annexure 7.

3.1 An overview of pharmacotherapy in the management of children with autism spectrum disorder at a public hospital in KwaZulu-Natal.

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Abstract

This study presents an overview of prescribing patterns and provides insight into the current management practice for the core symptoms and comorbidities of ASD in children. A quantitative retrospective study was conducted at a public hospital in KwaZulu-Natal, South Africa by reviewing patient files of children diagnosed with ASD and meeting the inclusion criteria for the study. A descriptive analysis of data was done to identify treatment trends and patient therapeutic outcomes. A total of 181 children met the inclusion criteria of the study. Risperidone was the most frequently prescribed drug (88%) for the management of comorbidities and/or core symptoms of ASD. Drugs prescribed to manage ASD comorbidities included methylphenidate, melatonin, sodium valproate, risperidone, oxybutynin, carbamazepine, and others. Except for risperidone, there were no additional drugs that targeted the core symptoms of ASD. Non-pharmacological therapies were often used collaboratively with medication to manage ASD symptoms. In 41% of patients, there were improvements in their symptoms (comorbidities and/or core symptoms).

Keywords: pharmacotherapy, therapeutic outcome, core symptom, comorbidity, autism

Introduction

Autism Spectrum Disorder (ASD) is a developmental disorder that involves impairment of social and communication abilities, restricted interests or repetitive behaviours, and challenges with sensory processing. The term "spectrum" reflects the fact that symptoms vary between individuals, ranging in type and severity (1).

To meet diagnostic criteria for ASD, according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), a child must have persistent deficits in each of three areas of social communication and interaction plus at least two of four types of restricted, repetitive behaviours (2). Proposed DSM-5 ASD criteria include three severity classifications: Level 1 ("Requiring support"), Level 2 ("Requiring substantial support"), and Level 3 ("Requiring very substantial support") (3). Prescribers often describe or identify level 1 as mild ASD, level 2 as moderate ASD, and level 3 as the most severe form of ASD (4, 5).

Medical comorbidities are more common in children with ASD than in the general population and can include epilepsy, macrocephaly, cerebral palsy, migraine/headaches, congenital abnormalities

of the nervous system, gastrointestinal disorders, sleep disorders, allergic disorders, and persistent neuroinflammation (6).

According to the World Health Organisation (WHO), approximately 1 in 100 children have ASD; however, these figures could be substantially higher based on results from additional well-controlled studies and the absence of ASD statistics in various low and middle-income countries (7). In South Africa, accurate local statistics for ASD are not available but it has been estimated that between 1% and 2% of the population may be affected by ASD (8).

The Food and Drug Administration (FDA) has approved the use of antipsychotic drugs, risperidone, and aripiprazole, for treating irritability associated with ASD in children. Other drugs are often used to improve symptoms of ASD, but are not approved by the FDA for this specific purpose; these include selective serotonin reuptake inhibitors, tricyclic antidepressants, stimulants, anticonvulsants, antipsychotics, and anti-anxiety medication (9). There are no approved medications for ASD core symptoms; however, given the significant clinical need, individuals with ASD are prescribed medication off-label for core or associated conditions, sometimes based on limited evidence for effectiveness (10).

Although some studies have evaluated and reviewed the pharmacological management of ASD (11, 12), there is limited data available on the pharmacological management of ASD in South Africa and Africa. The only known study in South Africa that assessed the prevalence and patterns of medication use in children with ASD was conducted almost a decade ago and utilised a survey questionnaire (13).

This study aims to review pharmacological treatment options used in the management of ASD in children at a public hospital in KwaZulu-Natal by identifying pharmacological therapeutic agents prescribed and determining their role and impact on treatment outcomes.

Methodology

Study design and setting

A retrospective descriptive study was carried out to determine the pharmacological management of children diagnosed with ASD. The study setting was a public sector referral hospital located in the KwaZulu-Natal province of South Africa. This hospital was initially built in 1928 as the first

facility in Africa dedicated exclusively to the treatment of children. A neuro-developmental assessment centre is located at the hospital and comprises specialised paediatric neurologists and a multidisciplinary team that manages children diagnosed with ASD and other neurological disorders.

Study target population and sampling strategy

Inclusion criteria

Patient files that met the following criteria were included in the study:

- Male and female individuals diagnosed with ASD (at all levels of severity).
- Children and adolescents between the age group of 2 and 17 years of age.
- ASD individuals with hospital visits between 01 January 2019 to 31st January 2022.
- ASD individuals with any type of medical comorbidity

Exclusion criteria:

- Neurology patients who were not on the autism spectrum according to the DSM-5 criteria (14)
- ASD patients who have not been prescribed any type of medication to manage the core symptoms or comorbidities.
- Individuals over the age of 17.

A total of 181 patients met the inclusion criteria and this sample size was deemed large enough to allow a detailed analysis of the pharmacological management of ASD.

Data collection

Patient medical files were the primary data source. A data extraction template was used to enter all required information for the retrospective study. The age, gender, and information related to name, dose, and frequency of medication/s prescribed were recorded. The prescriber's notes on the patient's progress and therapeutic outcomes were also obtained from the patient's medical file. An improvement or decline in the patient's condition was noted as an indicator of the therapeutic outcome. ASD-related comorbidities that warranted pharmacological treatment were determined from the patient file and were also identified by the class of drugs prescribed to treat a particular condition. Additionally, non-pharmacological interventions in the form of rehabilitation (speech,

occupational, or behaviour therapy) were obtained from the patient's file and recorded on the data template.

Data analysis

Data were analysed using descriptive statistics and presented in the form of frequency tables and bar and column graphs. T-tests were conducted to determine the probability (p-value) of results when required. To eliminate bias, data were collected utilising a pre-designed tool and the extraction of data was performed solely by the corresponding author of the study, with no assistance from medical staff who prescribed or dispensed the medication. The study eliminated selection bias by including all available patient files, dating from 01 January 2019 to 31 January 2022, meeting the inclusion criteria of the study.

Data confidentiality and ethical approval

To maintain confidentiality, no information that could identify patients was extracted during the data collection process. Since this study obtained retrospective information from patient files, with no direct contact with patients, informed consent was not required. Ethical approval and consent for access to the patient files were obtained from the Biomedical Research and Ethics Committee (BREC) of the University of KwaZulu-Natal (UKZN), the provincial office of the KwaZulu-Natal Department of Health (KZN-DOH) and the eThekwini district office of KZN-DOH.

Results

Demographic and general characteristics of the study

The final study sample consisted of 181 patient files and the demographic data is presented in Table 1. In this study, the ASD gender ratio was found to be approximately 3:1 with males consisting of 77% of the study sample compared to 23% of females. The ages of children diagnosed with ASD were between 2 and 13 years old with the majority of children presenting to the hospital between 4 and 6 years of age (61%).

Table 1: The Demographic Characteristics of the Sample (n = 181)

Characteristics of Children		Number	%
Sex	Male	139	77
	Female	42	23
Age Groups	2 – 3 years	24	13
	4 – 6 years	111	61
	7 – 9 years	40	22
	10 – 13 years	6	3
ASD Level of Severity	Mild (Level 1)	32	18
	Moderate (Level 2)	111	61
	Severe (Level 3)	38	21

Medication prescribed for children diagnosed with ASD

Table 2 provides a detailed list of all medications prescribed to children with ASD and includes the drug class, dosing range, therapeutic indication, and frequency of use. Risperidone was the most frequently prescribed drug (88%), followed by methylphenidate (32%) and sodium valproate (16%). Examples of common medication classes prescribed were antipsychotics (risperidone), anticonvulsants (lamotrigine, sodium valproate, topiramate, and levetiracetam), stimulants (methylphenidate), and mood stabilisers (carbamazepine).

Table 2: List and Characteristics of Medication Prescribed

Name of Medication	Medication Class	Dosing Range	Therapeutic Indication in Study	Frequency of Drug Choice
Risperidone	Antipsychotic	0.1mg – 2mg	Irritability, aggression, disruptive behaviour, sleep dysregulation, hyperactivity symptoms, and core symptoms of ASD	n = 159 (88%)
Aripiprazole	Antipsychotic	2,5mg – 5mg	Indicated for use in the absence of response to risperidone.	n = 1 (0, 6%)
Citalopram	Antidepressant	10mg	Anxiety, self-injurious and obsessive-compulsive behaviours	n = 2 (1, 1%)
Sodium Valproate	Anticonvulsant	120mg – 400mg	Epilepsy	n = 29 (16%)
Carbamazepine	Anticonvulsant	40mg – 200mg	Epilepsy, sleep dysregulation,	n = 17 (9%)

			or as a mood stabiliser	
Lamotrigine	Anticonvulsant	5mg – 75mg	Epilepsy	n = 8 (4, 4%)
Topiramate	Anticonvulsant	6,25mg – 75mg	Epilepsy	n = 6 (3, 3%)
Levetiracetam	Anticonvulsant	125mg – 500mg	Epilepsy	n = 3 (1, 7%)
Clonazepam	Benzodiazepine	0,1mg – 0,6mg	Epilepsy	n = 4 (2, 2%)
Methylphenidate	Stimulant	2,5mg – 20mg	Attention Deficit Hyperactivity Disorder (ADHD), hyperactive symptoms, reduced attention span, and concentration problems	n = 58 (32%)
Clonidine	Alpha Agonist	0,25mg	Sleep dysregulation or hyperactivity	n = 7 (3, 9%)
Melatonin	Sedative	3mg	Sleep dysregulation	n = 5 (2, 8%)
Oxybutynin	Anticholinergic	5mg – 10mg	Enuresis	n = 4 (2, 2%)
Cetirizine	Antihistamine	5mg – 10mg	Allergic rhinitis	n = 4 (2, 2%)

Fluticasone nasal spray	Steroid	unknown	Allergic rhinitis	n = 3 (1, 7%)
Lactulose	Laxative	5ml – 10ml	Constipation	n = 8 (4, 4%)
Liquid Paraffin	Laxative	5ml	Constipation	n = 1 (0, 6%)
Folic Acid	Vitamin B9	2,5mg – 5mg	As a dietary supplement when sodium valproate was prescribed.	n = 7 (3, 9%)

The pharmacological management of ASD-related comorbidities

The comorbidity mostly present in children diagnosed with ASD was hyperactivity or ADHD (57%). The most frequent pharmacological agents prescribed to manage the associated ADHD included risperidone (51%), methylphenidate (58%), and clonidine (4%). Irritability, aggression, or disruptive behaviour, appearing in 27% of study subjects, was managed with risperidone.

Sleep dysregulation also appeared frequently (22%) in children diagnosed with ASD and the therapeutic agents prescribed to manage this condition were melatonin (13%), clonidine (8%), risperidone (73%), or carbamazepine (8%), administered at night.

Epilepsy occurred in 16% of study subjects and was mostly managed with sodium valproate (97%) as monotherapy or in combination with other anticonvulsants including lamotrigine (27%), topiramate (20%), carbamazepine (13%), clonazepam (13%), or levetiracetam (10%).

Constipation was reported in 4% of children in the study and was managed by non-pharmacological agents in the form of lactulose (89%) or liquid paraffin (11%).

Other ASD comorbidities that required pharmacological intervention were allergic rhinitis (treated with cetirizine and/or fluticasone nasal spray) and nocturnal enuresis (treated with oxybutynin). Citalopram, an antidepressant, was prescribed for two children that displayed self-

injurious behaviour. Figure 1 provides an overview of the most frequent comorbidities experienced by children with ASD.

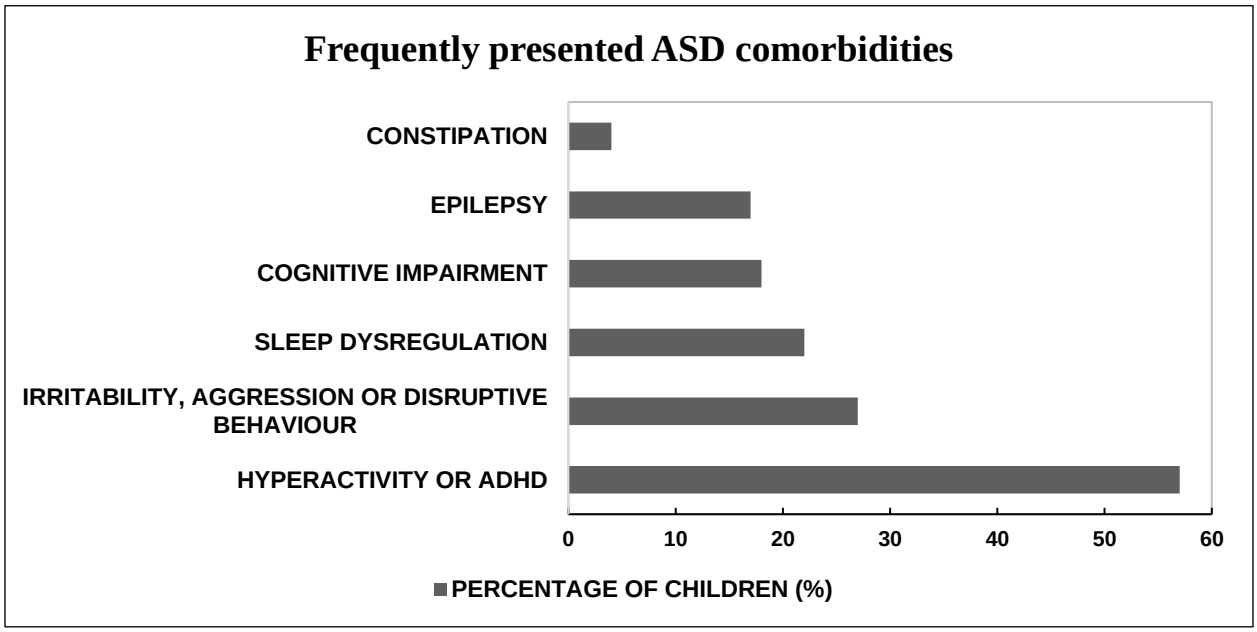

Figure 1: Common ASD comorbidities, presented by children in the study

The prescribing of psychotropic drug combinations

In this study, examples of psychotropic drugs prescribed included risperidone, aripiprazole, citalopram, clonazepam, methylphenidate, melatonin, and carbamazepine. Figure 2 illustrates the relationship between age, gender, and the prescribing of two or more psychotropic drugs. Most children in the 2 – 3-year-old age group were prescribed risperidone as monotherapy to control ASD symptoms; however, there were 2 male children in this age group that was prescribed methylphenidate (n = 1) or melatonin (n = 1) in addition to risperidone.

In the 4 – 6-year age group, combination prescribing was very similar when comparing males (29%) to females (21%). In the 7 – 9-year age group, significantly more males were on two or more psychotropic drugs when compared to other age groups (p-value = 0.03). In older children (ages 10 -13), equal numbers of males and females were prescribed two or more psychotropic drugs. Additionally, figure 2 also illustrates the percentage of children prescribed a single psychotropic drug to manage ASD symptoms. This percentage decreased as the age of the child

increased as shown with the highest percentage seen in the 2 -3-year-old age group and the lowest in the 7 – 9-year-old age group. This demonstrates the need for combination psychotropic drugs as the age of the child increased. The children in the 10 – 13-year-old age group however did not follow this trend since 50 % of children were prescribed methylphenidate as a single agent, mainly for challenges with concentration at school. This could be an indication of psychiatric comorbidities that warrant the use of combination psychotropic drugs, possibly peaking in children between the ages of seven and nine however additional studies are required to confirm this.

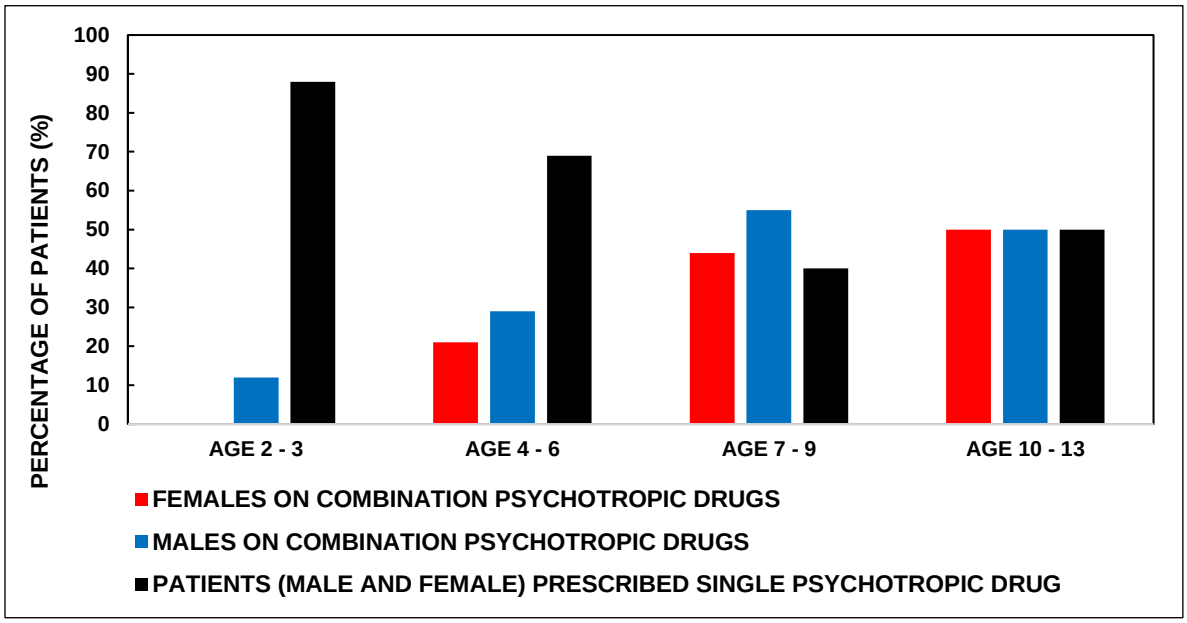

Figure 2: Relationship between age and gender and the percentage of children prescribed psychotropic drugs.

Therapeutic outcomes

The therapeutic outcomes for ASD management were obtained from prescriber progress notes in the patient files. In 41% (n = 74) of patients, there was a positive response to treatment due to an overall improvement in an ASD comorbidity and/or core symptoms from previous visits. In 20% of all patients, the core symptoms of ASD improved (defined by improvements in social communication, improved shared interest, and a decrease in repetitive behaviours).

Of the 41% (n= 74) of patients with improved treatment outcomes, 85% (n = 63) were prescribed risperidone. Other drugs associated with improved therapeutic outcomes included methylphenidate (34%), sodium valproate (19%), and carbamazepine (9%). These drugs were

either prescribed as monotherapy or in a combination with other drugs and/or non - pharmacological therapies.

Examples of qualitative comments from the prescriber related to improved therapeutic outcomes were; “hyperactivity and meltdowns have improved”, “behaviour has markedly improved on risperidone, he is no longer aggressive, now sleeps well and can also make 3-word sentences", “from the initial visit his aggressive behaviour has improved”, “he is now toilet trained and says occasional words”, “he has improved in his communication and stereotypic behaviour”, “sleep and hyperactivity have improved with risperidone”, “she has improved in communication, talks sentences, and methylphenidate improved her behaviour” and “his shared interest has improved from the last visit”.

In 31,5% (n = 57) of patients, there was a decline in their condition, described as worsening of symptoms, the need to increase doses of pharmacotherapy, and/or add on additional drug treatment/s and/or non-pharmacological therapies (speech, occupational, and behaviour therapy). Few patients (5%), displayed a negative response to methylphenidate as it either made the child's behaviour worst, resulted in a poor appetite, caused a deterioration in behaviour once the dose of the drug wore off, or displayed minimal effectiveness leading the prescriber to discontinue the drug. Additionally, there were a few patients (2, 8%), who were prescribed risperidone which either resulted in significant obesity, vomiting or caused a worsening of behaviour leading the prescriber to initiate alternative pharmacotherapy

In 21, 5% (n = 39) of patients, there were no notes related to treatment outcomes since their patient file only contained notes on an initial visit. These patients were either referred to their base hospital or would return for a review during the year.

In the balance of patients (n = 11), there were mixed comments related to therapeutic outcomes as the prescriber indicated that some symptoms improved yet others persisted and, for some patients, it was suggested that intensive non-pharmacological therapies be continued or commenced despite improvements in certain ASD comorbidities.

Discussion

This study provides an overview of the pharmacological management of ASD in children and adolescents through a retrospective review of patient medical files at a public hospital in KwaZulu-Natal, South Africa. A comprehensive list and description of pharmacological agents prescribed were analysed and reviewed.

While a number of pharmacological agents were found to be used in children with ASD, risperidone was the drug used most often. Risperidone is an FDA-approved agent for use in targeting the irritability and aggression associated with ASD in children (9). In this study, risperidone was prescribed to assist in the management of several comorbidities (irritability, aggression, disruptive behaviour, hyperactivity, and insomnia) as well as the core symptoms of ASD. Though its precise mechanism of action is not fully understood, the current focus is on the ability of risperidone to inhibit the D2 dopaminergic receptors and 5-HT2A serotonergic receptors in the brain (15). These dopamine and serotonin receptor antagonisms achieved by risperidone are believed to be responsible for the beneficial effects on ASD. The effects of risperidone on aggression, irritability stereotypes, tantrums, and restlessness can be attributed to dopamine antagonism. The effects on communication skills, restricted activity patterns and the ability to respond emotionally and socially can be considered a result of serotonin antagonism (16).

Although both risperidone and aripiprazole are FDA-approved agents for use in ASD (17), aripiprazole was only prescribed after consultation with a psychiatrist for a single patient with severe ASD who did not respond to risperidone. The limited use of aripiprazole would be an indication of adherence to standard treatment guidelines in South Africa, which lists risperidone as the only drug for the management of irritability, aggression, or self-injurious behaviour in children diagnosed with ASD (18). The switch from risperidone to aripiprazole in this study is in line with an international prospective study which concluded that aripiprazole might be generally well tolerated and may constitute an alternative treatment for individuals with ASD who experience poor efficacy or tolerability issues with risperidone treatment (19).

In addition to risperidone, methylphenidate was also frequently prescribed to children in the study. This could be due to 57% of children presenting with ADHD or hyperactivity symptoms. Methylphenidate is pharmacologically classified as a stimulant and is widely used as the first-line

treatment in children with ADHD. The mechanism of action of methylphenidate is related to the release of dopamine and norepinephrine in the central nervous system (20). Various international studies (21-23) also support the use of methylphenidate to manage hyperactivity and ADHD symptoms in children diagnosed with ASD.

Sodium valproate was also a frequently prescribed drug (16%) and indicated for the management of epilepsy or seizures in this study. A variety of other drugs were also prescribed to manage epilepsy symptoms and included lamotrigine, clonazepam, levetiracetam, and topiramate. Epilepsy is reported to co-occur in individuals with ASD and studies across the world have found prevalence estimates ranging from 4 to 38 % (24). Additionally, several lines of evidence point to valproate, lamotrigine, and levetiracetam as the most effective and tolerable anti-epileptic drugs for individuals with ASD (25). Although there are limited studies on the pharmacological management of epilepsy in children diagnosed with ASD, there is no evidence that seizures in children with ASD respond any differently to anti-epileptic drugs than seizures in children without ASD (26).

Cognitive impairment appeared in 16% of study subjects with ASD; however, it was unclear if any medication was prescribed to directly influence the management of this impairment. Additionally, neurodevelopmental regression appeared in 4% of children in this study. This condition is characterised by an initial normal social, emotional, and language development followed by loss of speech and social skills for no discernible reason (27). All children that presented with this condition were prescribed risperidone, either to treat additional comorbidities that the child presented with, and/or positively influence the symptoms of this condition. An interesting yet distressing observation was that a large number of children (48%) presented with two or more medical comorbidities simultaneously. According to the DSM-5, 70% of the time a diagnosis of ASD is accompanied by an additional comorbidity, and 40% of the time by two or more additional comorbidities of diagnosis (28). Additionally, an international study conducted to investigate the possibility of predictive patterns of ASD comorbidities in children, found there was an increased risk for seizures and sleep problems to co-occur with gastric disturbances, and behavioural impairments were also more severe as the number of co-occurring medical symptoms increased (29).

Common psychiatric comorbidities presented by children in this study included ADHD, aggression, disruptive behaviour, irritability, sleep dysregulation, anxiety, self-injurious behaviour, cognitive impairment, and neuro regression. Psychotropic medications are frequently used to target psychiatric symptoms in children with developmental conditions, despite limited evidence for their efficacy therefore clinicians should always use these drugs with caution, carefully weighing risks and benefits, and as a part of a comprehensive personalized approach (30). In this study, the likelihood of psychotropic drug combinations among children with ASD was highest among the 7 – 9-year-old age group ($p = 0.03$) and it was also evident that males across all age groups required a combination of psychotropic drugs more often than females. This is in line with a recent study that concluded that during early childhood, girls with ASD tend to show a greater reduction and less rise in their ASD symptom severity than boys with ASD (31).

The core symptoms of ASD recorded in this study included restricted, repetitive behaviours and social communication challenges. Despite the limited treatment options for ASD core symptoms, 20% of children displayed significant improvements in social communication impairments and/or restricted repetitive behaviours and the majority (83%) of them were prescribed risperidone either to target the core symptoms of ASD and/or manage a comorbidity. Various international studies also support the use of risperidone for the management of the core symptoms either as monotherapy (32) or with the addition of other therapeutic agents (33, 34). Targeting the core symptoms of ASD is of vital importance as these symptoms define ASD. A suggestion would be for prescribers to research current literature available regarding additional effective pharmacological management options for ASD core symptoms. As an example, recent clinical trials that utilise therapeutic agents like bumetanide (35), intranasal oxytocin (36), guanfacine (37), intranasal vasopressin (38), vitamin D (39), and omega fatty acids (40) have all demonstrated promising results on the core symptoms of ASD. It's important to note that these therapeutic agents are still under study and evaluation and their usage to manage the core symptoms of ASD also depends on the availability of a drug in a particular country.

It is important to highlight the use of non – pharmacological therapies in conjunction with pharmacotherapy in the management of ASD in children. Non-pharmaceutical therapy can effectively relieve the core symptoms of ASD, has fewer side effects than drugs, and is easily accepted by patients (41). In this study, 44% of patients were receiving speech and/or occupational

therapy and in 23% of patients, these types of therapies were recommended by the prescriber. Currently, no medication can cure ASD or manage all of its symptoms, however, research shows that medication is most effective when used in combination with behavioural therapies (42).

Previous international studies on the pharmacological management of ASD focus mainly on psychotropic drug use (43-45) while other studies involve reviews on drug treatment for a single type of ASD comorbidity (46-48) or an additional study focused on the prevalence of co-occurring conditions and medication use in the management of comorbidities among individuals with ASD (49). This study provides a review of the pharmacological management of comorbidities and core symptoms of ASD, therapeutic outcomes, and psychotropic drug usage in children diagnosed with ASD. Additionally, the results from the study were compared to various international trends. Interestingly, this is also the first known type of study to be conducted in a clinical setting in South Africa. This is taking into consideration, the study in the Western Cape related to the pharmacological management of ASD, conducted almost a decade ago in a school with a sample size of 65 pupils (13). As a recommendation, additional studies could be conducted in other provinces and could also include the private sector to obtain a more generalised summary of the role of pharmacotherapy in the management of ASD in South Africa.

Limitations

The results of this study are from a single hospital based in one district of the province of KwaZulu-Natal, however, this was a referral hospital and included patients from different locations throughout the province. The study was conducted in a public hospital setting therefore the therapeutic agents prescribed may differ from a private hospital setting as public hospitals in South Africa are required to adhere to standard treatment guidelines (18) and essential drug lists (18) when prescribing medication.

The study included a review of patient files with initial hospital visits from January 2019 to January 2022 only, therefore it does not reflect the total number of ASD patients that have visited the hospital. Additionally, the hospital utilises a manual filing system and this presented the challenging task of searching through the medical records of every patient that visited the hospital to locate patients that met the study inclusion criteria. Furthermore, medical records were filed according to the child's date of birth, and ASD patients were not filed separately from patients with

other types of neurological disorders. Due to these challenges with locating patients, it is difficult to interpret the 181 patients included in the study as an exact numerical representation of patients that met the inclusion criteria for this study.

Summary

The pharmacological management of Autism Spectrum Disorder (ASD) remains a challenge due to limited effective treatment options, the Food and Drug Administration's (FDA) approval of only two drugs (9) , and the absence of drugs that can cure the core symptoms (10). In South Africa, little is known about the role of pharmacotherapy in the management of children diagnosed with ASD. This study provided insight into the current pharmacological management of ASD in children at a KwaZulu-Natal hospital.

Risperidone was the most frequently prescribed drug (88%) for the management of comorbidities and/or core symptoms of ASD. This study also provided sufficient information to gain clarity on the role of pharmacotherapy in the management of ASD. Based on the results of this study, various drugs (for example risperidone, methylphenidate, sodium valproate, oxybutynin, melatonin, and others) play a prominent role in managing and improving common ASD-related comorbidities like irritability, aggression, sleep dysregulation, epilepsy, ADHD and nocturnal enuresis. There was a challenge regarding limited treatment options for ASD core symptoms however this was expected considering there are still no approved therapeutic agents that can cure these symptoms (10). Although a few patients that were prescribed risperidone experienced improvements in the core symptoms of ASD, the direct role of pharmacotherapy in the management of ASD core symptoms remains questionable. The frequent prescribing of 2 or more psychotropic drugs to manage psychiatric comorbidities (for example aggression, self-injurious and disruptive behaviour, irritability, and ADHD) in this study is also a noteworthy area of concern as these drugs come with high side effect profiles and their use should be limited to when the benefit outweighs the risk to the child.

From the results of this study, 41% of patients achieved a positive prognosis and this percentage could improve depending on the therapeutic outcomes for children with initial visits. As the availability and use of effective drugs (including vitamin, mineral, and dietary supplements) for the management of ASD core symptoms increases and with the collaborative use of intensive non-

pharmacological interventions, it is safe to conclude that substantially greater therapeutic outcomes could be achieved for children diagnosed with ASD in South Africa.

Disclosures and Declarations

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Author's contribution statement

All the listed authors contributed significantly to the design, implementation, and development of the manuscript. The principal researcher (also the corresponding author) was responsible for data collection, analysing, and interpretation of the data obtained and for the writing of the article. The co-authors were responsible for reviewing, editing, and approving the contents of the article.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data Confidentiality and Ethical approval

To maintain confidentiality, no information that could identify patients was extracted during the data collection process. As this study obtained information from patient files, with no direct contact with patients, informed consent was not needed. Ethical approval was obtained from the Biomedical Research and Ethics Committee (BREC), UKZN (Reference number - KZ_202112_018) and KZN Department of Health (KZN-DOH). Consent for access to the

patients' files was sought from the Medical Management of the public hospital which is managed from the district office of KZN

Chapter Summary

This chapter provided an overview of pharmacotherapy in the management of children diagnosed with ASD at a public hospital facility in KwaZulu-Natal, South Africa. The following chapter concludes the study.

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Chapter 4 - Conclusion

This final chapter highlights the overall findings of both the retrospective and systematic review components of the study. Additionally, the significance, strengths and limitations of the study is highlighted and recommendations for future research included.

4.1. Summary of findings

This study aimed to review pharmacological treatment options used in the management of ASD in children and adolescents. To achieve this, the following objectives were met:

- A systematic review of pharmacological management options for ASD in children and adolescents was conducted with emphasis on effective randomised clinical trials that were conducted internationally over the past decade.
- A retrospective review of drugs included in the management of children with ASD at a public hospital in KwaZulu-Natal was conducted.
- The identification of the most common ASD comorbidities that required pharmacological treatment including a review on psychotropic drug use was highlighted and discussed.
- A discussion on pharmacotherapy options for the management of ASD core symptoms
- A review of therapeutic outcomes in children with ASD, receiving pharmacological management at the public hospital institution.
- The comparison between the pharmacological management of ASD in KwaZulu-Natal with various international trends.

Summary of findings based on each objective

- This systematic review successfully summarized the pharmacological advancements made in the past decade to manage ASD in children through 33 articles based on effective randomised control trials and via 4 medical databases (PubMed, PsycInfo, Scopus and Science Direct). Various drugs displayed promising therapeutic outcomes when compared to placebos for the management of ASD-related comorbidities and some examples of these drugs included risperidone (DeVane et al., 2019), aripiprazole (Ichikawa et al., 2017), methylphenidate (Scahill et al., 2017), guanfacine (Politte et al., 2018), and levetiracetam (M. Wang et al., 2017) . Bumetanide was the most frequently used agent for its

effectiveness in managing the core symptoms of ASD, as reported by 4 randomised control trials (Dai et al., 2021; Lemonnier et al., 2012; Lemonnier et al., 2017; Sprengers et al., 2021) in the systematic review. Other effective drugs for the management of ASD core symptoms included buspirone (Chugani et al., 2016) , fluoxetine (Reddihough et al., 2019), intranasal oxytocin (Parker et al., 2017), intranasal vasopressin (Parker et al., 2019), and prednisolone (Brito et al., 2021) . Clinical trials evaluating the use of dietary and vitamin supplements (vitamin D (Mazahery et al., 2020), omega fatty acids (Doaei et al., 2021), or folic acid (Frye et al., 2018)) also produced improved therapeutic outcomes for the management of ASD comorbidities and/or core symptoms.

- Risperidone was the most frequently prescribed drug (88%) in the retrospective hospital study, followed by methylphenidate (32%) and sodium valproate (16%). Examples of common medication classes prescribed were antipsychotic (risperidone), anticonvulsants (lamotrigine, sodium valproate, topiramate, and levetiracetam), stimulants (methylphenidate), and mood stabilisers (carbamazepine). Other therapeutic agents prescribed included melatonin, lactulose, liquid paraffin, and folic acid. Various individuals in the study were also receiving non-pharmacological interventions as an adjunct to pharmacotherapy; this included speech, occupational, and behaviour therapy.

- Examples of frequent ASD comorbidities presented by children in this study, warranting pharmacological treatment, were attention deficit hyperactivity disorder (57%), irritability, aggression or disruptive behaviour (27%), sleep dysregulation (22%), and epilepsy (17%). Therapeutic agents that were prescribed to manage ASD comorbidities included, but were not limited to, risperidone, methylphenidate, sodium valproate, carbamazepine, clonidine, melatonin, and oxybutynin. The most frequently prescribed psychotropic drug combination was risperidone and methylphenidate. In this study, the likelihood of psychotropic drug combinations among children with ASD was highest among the 7 – 9-year age group and it was also evident that males across all age groups (except for the 10 -13-year age group with the same percentage of male and female) required combination psychotropic drugs more often than females.

- The only drug prescribed to possibly influence the core symptoms of ASD was risperidone. Despite the limited treatment options for ASD core symptoms, 20% of children displayed significant improvements in social communication impairments and/or restricted repetitive behaviours and the majority (83%) of them were prescribed risperidone either to target the core symptoms of ASD and/or manage a comorbidity.

- The therapeutic outcomes for ASD children were obtained from prescriber progress notes in the patients' files. In 41% (n = 74) of patients, there was a positive response to treatment and 85% (n = 63) were prescribed risperidone. Additional drugs associated with improved therapeutic outcomes included methylphenidate (34%), sodium valproate (19%), and carbamazepine (9%). In 31, 5% (n = 57) of patients, there was a decline in their condition.

- The results of the retrospective study facilitated a comparison between the pharmacological management of ASD in South Africa with various international trends. Risperidone has FDA approval for use in irritability, aggression, and disruptive behaviour (DeFilippis et al., 2016) and was the most prescribed pharmacological agent to target these symptoms. Risperidone was also prescribed to target the core symptoms of ASD and the use of this drug for this purpose is in line with various international studies (Alsayouf et al., 2022; Alsayouf et al., 2021; Ghaeli et al., 2014). Aripiprazole has FDA approval for use in targeting the irritability and aggression seen in children with ASD (DeFilippis et al., 2016), however, it was only prescribed for one child in the study. This is due to its use being reserved for patients who do not respond to risperidone. The standard treatment guidelines of South Africa list risperidone as the only drug indicated for use in children diagnosed with ASD (Knowledge Hub, 2021).

  The use of various agents for the management of ASD-related comorbidities e.g. methylphenidate (used for ADHD), sodium valproate (used to control seizures), melatonin (to manage insomnia), cetirizine (for allergic rhinitis), oxybutynin (nocturnal enuresis), were all in line with the pharmacological indication for its use.

  Constipation was the only gastrointestinal complication experienced by children in the study and therapeutic agents to manage this comorbidity was limited to lactulose and liquid paraffin. The health benefits of probiotics, as indicated by several studies (Arnold et al.,

2019; Niu et al., 2019; Shaaban et al., 2018), discussed in the systematic review, should also be taken into consideration when managing gastrointestinal complications in children with ASD.

Except for risperidone, the retrospective study identified no other drugs that targeted the core symptoms of ASD. The results of the systematic review (based on international clinical trials) have however listed various therapeutic agents with promising effects on the core symptoms of ASD.

4.2. Significance of the Study

There are no known studies investigating the pharmacological management of ASD in children in the province of KwaZulu-Natal, South Africa. Additionally, the only known study to be conducted in South Africa or Africa, based on the use of pharmacotherapy for the management of children diagnosed with ASD, was done almost a decade ago in the Western Cape (Louw et al., 2012) . Some of the challenges faced by children with ASD include the absence of a pharmacological cure as evidenced by the FDA approval of only 2 drugs. This study provides insight and an overview of pharmacotherapy in the management of children diagnosed with ASD at a public hospital in KwaZulu-Natal. The results of the study provide clarity on prescribing patterns, therapeutic outcomes and facilitated a comparison with various international trends. The systematic review facilitated the identification of promising pharmacological agents for the management of both the core symptoms and comorbidities of ASD in children and adolescents.

4.3. Strengths of the Study

The retrospective study is the first known type of study to be conducted in a clinical setting in South Africa. Various international studies based on the pharmacological management of ASD focussed on comorbidities (Harstad et al., 2021; Parikh et al., 2008; F. Wang et al., 2021) or psychotropic drug use only (Gannon et al., 2021; Ritter et al., 2021; Rosenberg et al., 2010) . This study provided an overview of pharmacotherapy for the management of ASD core symptoms and comorbidities, investigated psychotropic drug usage, discussed patient therapeutic outcomes and utilised the results to facilitate a comparison with international trends. Additionally, the systematic review is also the first study that has identified pharmacological agents (for managing both the

core symptoms and comorbidities of ASD) based on successful randomised control trials over the past decade.

4.4. Limitations

The systematic review was limited to full-text studies from four databases and eligible studies were selected from 01 January 2012 to 01 January 2022 only. In addition, due to the large volume of studies available on the pharmacological management of ASD, the eligibility criteria for study design were limited to randomized control trials, and data analysis was limited to narrative synthesis due to the heterogeneous nature of the studies retrieved.

The results of the retrospective study are from a single hospital based in one district of the province of KwaZulu-Natal. The study included a review of patient files with initial hospital visits from January 2019 to January 2022 only, therefore it does not reflect the total number of ASD patients that have visited the hospital. Due to challenges with locating patients from a large manual filing database, it is difficult to interpret the 181 patients included in the study as an exact numerical representation of patients that met the inclusion criteria for this study.

4.5. Recommendations

Regarding the systematic review, additional therapeutic agents that display effectiveness through open-label trials, case reports, case studies, and other types of study designs should also be taken into consideration. As additional studies are conducted on the pharmacological management of ASD, a meta-analysis for individual drug effectiveness can be performed.

Additional studies, similar to the retrospective hospital study, could be conducted in other provinces and should also include the private sector to obtain a more generalised summary of the role of pharmacotherapy in the management of ASD in South Africa. This recommendation could also be extended to the continent of Africa since there are no known studies that review or analyse the pharmacological management of ASD in children. Additional studies could also focus on close tracking the effect of drugs on therapeutic management, or studies involving interviewing rehabilitation professionals for discussion of the impact of medication on progress in therapy.

Regarding the pharmacological management of the core symptoms of ASD in KwaZulu-Natal or South Africa as a country, further research on the availability of effective therapeutic agents

against the core symptoms of ASD should be conducted. As highlighted in the systematic review, various pharmacological agents display promising effectiveness including the use of dietary and vitamin supplements which are widely available.

4.6. Conclusion

The systematic review has successfully summarised the pharmacological advancements made in the past decade to manage ASD core symptoms and comorbidities. In the future, based on results from additional studies conducted internationally, there is a possibility that bumetanide and possibly other therapeutic agents included in the systematic review, would be in a position to obtain regulatory approval for use in ASD.

The retrospective hospital study provided insight into the pharmacological management of ASD in children treated at a public hospital facility. Sufficient information was obtained to gain clarity on medication prescribing patterns and to also conclude that pharmacotherapy does play an important role in the management of ASD comorbidities. There is a challenge as limited treatment options for ASD core symptoms are available; risperidone was the only agent prescribed to possibly influence these symptoms. With the increasing use of psychotropic drugs in children with ASD, prescribers must utilise these drugs only when the benefit to a child outweighs the possible risks associated with the drug. Considering there is still no cure for ASD, the management of children with ASD at the public hospital did produce favourable outcomes in 41% of all children included in the study. As more effective pharmacological agents (including vitamin, mineral, and dietary supplements) become available and approved for use in managing ASD core symptoms and with the adjunctive use of intensive non-pharmacological therapies, a further improved prognosis for children diagnosed with ASD might be achievable.

Chapter Summary

This chapter highlighted important aspects of the study and summarised the main findings which all serve as an important contribution to research based on the pharmacological management ASD in children and adolescents.

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Annexure 1: Ethical approval letter from the University of KwaZulu-Natal's (UKZN) Biomedical Research and Ethics Committee (BREC)

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

04 February 2022
Miss Jennal Maniram (200303093)
School of Health Sciences
Westville

Dear Miss Maniram,
Protocol reference number: BREC/00003667/2021
Project title: An Overview of Pharmacotherapy in the Management of Children with Autism Spectrum Disorder at a Public Hospital Facility in KwaZulu-Natal.
Degree: Masters

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application.

The conditions have been met and the study is given full ethics approval and may begin as from 04 February 2022. Please ensure that any outstanding site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is subject to national and UKZN lockdown regulations, see (http:research.ukzn.ac.za/Libraries/BREC/BREC_Ammended_Lockdown_Level_1_Guidelines.sflb.ashx). Based on feedback from some sites, we urge PIs to show sensitivity and exercise appropriate consideration at sites where personnel and service users appear stressed or overloaded.

This approval is valid for one year from 04 February 2022. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2020) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678). The sub-committee's decision will be noted by a full Committee at its next meeting taking place on 08 March 2022.

Yours sincerely,

[redacted]

Prof D Wassenaar (Chair: Biomedical Research Ethics Committee)

Annexure 2: Letter of approval from the KZN Department of Health

KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:
Health Research & Knowledge Management Unit

Postal Address: Private Bag X9050
Physical Address: 330 Langalibalele Str; PM Burg; 3201
Tel: 0333953189/3123/2805 Fax: 033-3943782
Email address: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

NHRD Ref: KZ_202112_018

Dear Ms J Maniram
(UKZN)

Approval of research

1. The research proposal titled **'An Overview of Pharmacotherapy in the Management of Children with Autism Spectrum Disorder at a Public Hospital Facility in Kwa-Zulu Natal.'** was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

   The proposal is hereby **approved** for research to be undertaken at KZN Children's hospital.

2. You are requested to take note of the following:

   a. *All research conducted in KwaZulu-Natal must comply with government regulations relating to Covid-19. These include but are not limited to: regulations concerning social distancing, the wearing of personal protective equipment, and limitations on meetings and social gatherings.*
   b. *Kindly liaise with the facility manager BEFORE your research begins in order to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.*
   c. *Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.*
   d. *Provide an interim progress report and final report (electronic and hard copies) when your research is complete to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za*
   e. *Please note that the Department of Health shall not be held liable for any injury that occurs as a result of this study.*

For any additional information please contact Ms G Khumalo on 033-395 3189.

Yours Sincerely

[redacted]

Dr E Lutge
Chairperson, Health Research Committee
Date: 18/01/2022

Annexure 3: Letter of approval for access to KZN Children's Hospital

KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE: Monitoring and Evaluation
Physical address: 83 King Cetshwayo Highway; Highway House; Mayville 4091
Postal Address: private Bag X 54318, Durban 4000 eThekwini District Office
Tel: 031 240 5308 Fax: 031 240 5555 Email: Ntombenhle.Ngcobo@kznhealth.gov.za
www.kznhealth.gov.za

Enquiries: Mrs. N.P Ngcobo
Date: 09/11/2021

Ms J Maniram
University of Kwa Zulu Natal

RE: SUPPORT FOR RESEARCH STUDY "AN OVERVIEW OF PHARMACOTHERAPY IN THE MANAGEMENT OF CHIILDREN WITH AUTISM SPECTRUM DISORDER (ASD) AT A PUBLIC AND PRIVATE HOSPITAL FACILITY IN KWA ZULU NATAL."

I have pleasure in informing you that the District is granting you support to conduct the research study titled **"An overview of Pharmacotherapy in the Management of Children with Autism Spectrum Disorder (ASD) at a Public and Private Facility in Kwa Zulu Natal"** at eThekwini Health District Facilities.

Please note the following:

1. Please ensure you adhere to all the policies, procedures, protocols and guidelines of the department of health with regards to this research.
2. This research will only commence once this office has received confirmation from the provincial health research committee in the KZN department of health. Online application must be done in the following site, https://nhrd.health.gov.za
3. Please ensure this office is informed before you commence your research.
4. The District office/facility will not provide any resources for this research.
5. You will be expected to provide feedback on your findings to the district office/facility.

Thank you.

Sincerely,

[redacted]

Mrs. N.P. Ngcobo
(P, Monitoring and Evaluation Manager)
EThekwini Health District

GROWING KWAZULU-NATAL TOGETHER

Annexure 4: Confirmation of submission and publication of manuscript I to the journal: Neuropsychiatric Disease and Treatment

Manuscript submitted to Dove Medical Press

Mrs Whimp <deidrewhimp@dovepress.com> Fri, 15 Apr 2022 at 13:13

Reply to: Mrs Whimp <deidrewhimp@dovepress.com>

To: Miss Maniram <jennalmaniram@gmail.com>

Dear Miss Maniram,

Thank you for your recent submission to Neuropsychiatric Disease and Treatment, titled "Pharmacological Management of Core Symptoms and Comorbidities of Autism Spectrum Disorder in Children and Adolescents: A Systematic Review" which has been received.

You uploaded the following files with this submission:

371013-ms.docx

371013-figure-1-summary-of-study-selection-procedure.pdf

371013-appendix-3-study-appraisal-tool-.docx

371013-appendix-2-data-extraction-tool.docx

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The purpose of this form is to provide the Editor-in-Chief of Neuropsychiatric Disease and Treatment with important information about your possible conflicts of interests. The composition of this form follows that of the International Committee of Medical Journal Editors

(ICMJE) standard and further demonstrates our commitment to the highest ethical and professional standards. The form is designed to be completed and stored electronically. When the manuscript has been sent for peer review each author will receive an individual email like this and should submit a separate form. Each author is responsible for the accuracy and completeness of the submitted information.

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Please note that your submission has been received on the basis that you are in agreement with the terms and conditions which you were asked to consent to during the submission process. These are outlined again below and are available in full on the website (https://www.dovepress.com/author_guidelines.php?content_id= 772):

The submission is in compliance with the author guidelines and any applicable journal-specific guidelines; and,

- My co-authors (if any) have authorized me to submit our manuscript; and,
- I am not in a conflict of interest; and,
- I have read and understood the copyright terms; and,
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Many thanks for your submission.

Yours sincerely

Mrs Whimp (Editorial Team)

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(ID: 371013)

Your manuscript is published

Lucas Pratt <lucaspratt@dovepress.com> Sat, 06 Aug 2022 at 14:40

Reply to: Lucas Pratt <lucaspratt@dovepress.com>

To: Miss Maniram <jennalmaniram@gmail.com>

Dear Miss Maniram

I am happy to advise that your typeset manuscript has just been published in its final form on our website. You can view and download it here: https://www.dovepress.com/articles.php?article_id=77175.

Your paper has now completed our production processes. To help us improve our service we would be interested in your feedback on your experience. Please take a moment to respond to our quick author survey here:

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Management+of+Core+Symptoms+and+Comorbidities+of+Autism+Spectrum+Disorder+in+Children+an d+Adolescents%3A+A+Systematic+Review

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I would like to take this opportunity to personally thank you for your contribution to Neuropsychiatric Disease and Treatment. It was a pleasure working with you and I hope we can do so again in the near future. Yours sincerely

Lucas Pratt

Production Coordinator, Dove Medical Press Ltd

Dove Medical Press: Your paper is now on PubMed

Adrian Bell <adrianbell@dovepress.com> Thu, 25 Aug 2022 at 05:37

Reply to: Adrian Bell <adrianbell@dovepress.com>

To: Miss Maniram <jennalmaniram@gmail.com>

Miss Maniram

You will be pleased to hear that your paper "Pharmacological Management of Core Symptoms and Comorbidities of Autism Spectrum Disorder in Children and Adolescents: A Systematic Review" is now indexed on PubMed.

Link to your paper on PubMed: https://pubmed.ncbi.nlm.nih.gov/35968512/

If the link doesn't open when you click on it, please copy and paste the whole link into your web browser. I hope that you have enjoyed the experience of publishing with us and think of us when selecting a journal for your next paper. For your information our current manuscript processing averages 24 business days from receipt of manuscript to first editorial decision. From editorial acceptance to publication is 10 business days.

Best regards, Adrian Bell

Neuropsychiatric Disease and Treatment, Dove Medical Press

Annexure 5: Submission guidelines for Neuropsychiatric Disease and Treatment

Manuscript preparation

- While the editors fully understand the extra challenges posed to authors whose native language is not English, we must ask that all manuscripts be reviewed and edited by a native speaker of English with expertise in that area prior to submission
- Double-spacing
- 3-cm margins
- Page numbers
- Line numbers
- Clear concise language
- American spelling (all components of a manuscript must be in English)
- Ensure tables and figures are cited
- Manuscripts should be submitted in Microsoft Word format
- Use International Systems of Units (SI) symbols and recognized abbreviations for units of measurement
- Do not punctuate abbreviations eg, et al, i.e.
- Spell out acronyms in the first instance in the abstract and paper
- Word counts are not specified. In general, shorter items range from 1000 to 3000 words and reviews from 3000 to 7,500
- Generic drug names are used in title, text, tables, and figures
- Suppliers of drugs, equipment, and other brand-name material are credited in parentheses (company, name, city, state, country)
- If molecular sequences are used, provide a statement that the data have been deposited in a publicly accessible database, eg, GenBank, and indicate the database accession number
- Depositing laboratory protocols on protocols.io is encouraged, where a DOI can be assigned to the protocol. To include a link to a protocol in your manuscript:
  1) Describe your step-by-step protocol on protocols.io
  2) Select "Get DOI" to issue your protocol with a unique DOI (digital object identifier)
  3) Include the DOI link in the Methods section of your manuscript using the format provided

by protocols.io: http://dx.doi.org/10.17504/protocols.io.xxxxxxx (where xxxxxxx is the unique DOI)

At this stage, your protocol is only visible to those with the link. This allows editors and reviewers to consult your protocol when evaluating the manuscript. You can make your protocols public at any time by selecting "Publish" on the protocols.io website. Any referenced protocols will automatically be made public when your article is published.

Manuscript structure

Title page

- First name/given name(s) and last name/family name of authors (see Authorship section below)
- Author affiliations: department, institution, city, state, country
- ORCID number(s) for all authors whenever available
- If 2 or more authors on a paper contributed equally, please use the following format:

  Author name[1*]

  Author name[2*]

  Author name[3]

  *These authors contributed equally to this work

Abstract

There are two types of abstracts - structured and unstructured. Original research papers require a structured abstract. Both types of abstracts should be no more than 300 words.

Keywords

3–6 keywords

Corresponding author

Name, physical address, phone, fax, email

Introduction

Material and Methods

Results

Discussion

Conclusions

Abbreviations (if any)

Ethics approval and informed consent

All research studies on humans (individuals, samples or data) or animals must include a statement on ethics approval and, when human research is involved, consent. A statement confirming the name of the Institutional Review Board (IRB) or other appropriate ethics committee that approved the study must be included within the manuscript. The relevant reference/permit numbers should also be included. Please see our editorial policies for more information.

Consent for publication

Consent to publish statements must confirm that the details of any images, videos, recordings, etc. can be published, and that the person(s) providing consent have been shown the article contents to be published. Authors must be prepared to provide copies of signed consent forms to the journal editorial office if requested. Please see our editorial policies for more information.

Data availability (where applicable)

Please include a statement about where data supporting the results reported in the manuscript can be found and about data sharing including, where applicable, links to the publicly archived datasets. The statement of data availability should explain which additional unpublished data from the study, if any, are available, to whom, and how these can be obtained. In cases where authors do not wish to share their data or are unable to do so, they should state that data will not be shared and the reasons why. Please refer to our editorial policies for further information.

Funding

Please declare all the sources of funding including financial support. Please describe the role of the sponsor(s), if any, in any of the stages from study design to submission of the paper for publication. Please state if the sponsor(s) had no such involvement.

Please ensure that this information is accurate and in accordance with your funder's requirement.

Competing interests

Your relationship with other people or organizations may influence the way you interpret data or present the information in your study. This is known as a competing interest and all authors of a paper submitted to any Dove Medical Press journal are required to complete a declaration of competing interests. This includes all financial or non-financial competing interests which can include employment with the study sponsor, stock holdings or options, patents, royalties, personal fees, holding a board position, or any political, religious, or academic interest relevant to the published content. All competing interests will be listed in the declarations at the end of

the article.

Authors' contributions

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1. Made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas.
2. Have drafted or written, or substantially revised or critically reviewed the article.
3. Have agreed on the journal to which the article will be submitted.
4. Reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage.
5. Agree to take responsibility and be accountable for the contents of the article.

All authors must meet conditions 1, 2, 3, 4 and 5 and appropriate credit for each author's contribution should be given.

Acquisition of funding, data collection, or general team supervision alone does not constitute authorship.

Increasingly, authorship of multicenter trials is attributed to a group. All members of the group who are named as authors should fully meet the above criteria for authorship/contributorship.

The group should jointly make decisions about contributors/authors before submitting the manuscript for publication. The contact person should be prepared to explain the presence and order of these individuals. It is not the role of editors to make authorship/contributorship decisions or to arbitrate conflicts related to authorship.

Acknowledgments

All contributors who do not meet the criteria for authorship should be listed in the Acknowledgments section. Examples of who might be acknowledged include those who provided only technical help, writing assistance, or a department chairperson who provided only general support. Authors should declare whether they had assistance with the study design, data collection, data analysis, or manuscript preparation. If such assistance was provided, the authors should disclose the identity of the individuals who provided this assistance, with their permission, in the published article. Financial and material support should also be acknowledged.

Groups of persons who contributed materially to the paper but whose contributions do not justify authorship may be listed under such headings as “clinical investigators” or “participating investigators,” and their function or contribution should be described—for example, “served as scientific advisors”, “critically reviewed the study proposal”, “collected data”, or “provided and cared for study patients”. Because readers may infer their endorsement of the data and conclusions, these persons must give written permission to be acknowledged.

For individual members of a collaboration group to be searchable through PubMed (for those journals listed on PubMed), please ensure that the title of the collaboration group is included on the title page and in the submission system and also include collaborating author names as the last paragraph of the “Acknowledgments” section. Please add authors in the format First Name, Middle initial(s) (optional), Last Name.

As it takes PubMed additional time to code these groups these may not be present when an article is initially included on PubMed.

Authors' information (optional)

Information about the author(s) that may be relevant to the interpretation of the article may be listed here. This may include the authors’ affiliations, qualifications or other relevant background information. This section does not list any competing interests.

Reference Style Guidelines

DMP follow the style adopted by the American Medical Association (AMA), * (pp39–79) which, in turn, is based on the style developed by the International Committee of Medical Journal Editors in 1978 in Vancouver.

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Users of the EndNote® software should select the JAMA reference style when preparing references for any Dove Medical Press Journal. Please disable EndNote® before you submit your manuscript.

To disable EndNote® first save a copy of the document. Then in Word, use the EndNote® tab and click on "Convert Citations and Bibliography" and select "Convert to Plain text" This will remove the EndNote® encoding but leave the citations and bibliography.

Please note that authors are responsible for the accuracy and completeness of their references.

Text citations: Cite references sequentially in text, tables, and legends by superscript Arabic numerals with no parentheses, eg, [1] or [3,4] or [10–15]. Numbers should be placed **after** punctuation marks, eg, .[3,4]

Do not use Microsoft Word's footnote/endnotes function to build the reference list as this can introduce errors during the typesetting process.

Reference list: List items **numerically** (eg. 1, 2, 3, 4) in the order they are cited in the text, eg, 4. Kapur NK, Musunuru K. Clinical efficiency and safety of statins in managing cardiovascular risk. *Vasc Health Risk Manag*. 2008; 4(2):341–353.

Annexure 6: Confirmation of submission for manuscript II to the journal: Child Psychiatry and Human Development.

Child Psychiatry & Human Development - Receipt of Manuscript 'An overview of...'

1 message

Child Psychiatry & Human Development <jeyasri.varadarajan@springernature.com> Mon, 07 Nov 2022 at 09:24 To: Jennalmaniram@gmail.com

Ref: Submission ID 3c3246d7-4f6a-40a5-aee2-054eab8df719

Dear Miss J Maniram,

Thank you for submitting your manuscript to Child Psychiatry & Human Development.

Your manuscript is now at our initial Technical Check stage, where we look for adherence to the journal's submission guidelines, including any relevant editorial and publishing policies. If there are any points that need to be addressed prior to progressing we will send you a detailed email. Otherwise, your manuscript will proceed into peer review.

You can check on the status of your submission at any time by using the link below and logging in with the account you created for this submission:

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Kind regards,

Editorial Assistant, Child Psychiatry & Human Development

Annexure 7: Submission Guidelines for manuscript II to the journal: Child Psychiatry and Human Development.

CHILD PSYCHIATRY & HUMAN DEVELOPMENT

Instructions for Authors

Online

Manuscript Submission

Springer offers authors, editors, and reviewers of *Child Psychiatry & Human Development* the use of our fully web-enabled online manuscript submission and review system. The journal accepts only online submissions and the review system allows authors to track the review process of manuscripts in real time. Manuscripts should be submitted to http://chud.edmgr.com.

The online manuscript submission and review system for *Child Psychiatry & Human Development* offers easy and straightforward log-in and submission procedures. The system supports a wide range of submission file formats: for manuscripts-Word, WordPerfect, RTF, TXT, and LaTex; for figures-TIFF, GIF, JPEG, EPS, PPT, and Postscript. PDF is not an acceptable file format.

Manuscript Style

Length of article: Articles are expected to be no more than 35 double-spaced pages including all tables, figures, references, abstract and titles page. For comprehensive reviews, the page limit is 55 pages.

Typing Format: Double-spaced, 12 point font, pages numbered consecutively (except for figures). Two words from the Running Head may appear in the header of each page.

Title Page: A title page is to be provided and should include the title of the article, author's

name(s), and suggested running head. Academic affiliations of all authors should be included. The affiliation should comprise the department, institution (usually university or company), city, and state (or nation) and should be typed as a footnote to the author's name. For office purposes, the title page should include the complete mailing address including email address, telephone number, and fax number of the corresponding author designated to review feedback and proofs.

Abstract: An Abstract, no longer than 150 words, must be provided. No headings of any type can be used within the Abstract proper. The Abstract is to be the second page. A list of 4-5 Keywords is to be provided directly below the Abstract. Keywords should express the precise content of the manuscript, as they are used for indexing purposes.

Illustrations, Artwork, and Tables: 1llustrations (photographs, drawings, diagrams, and charts) are to be numbered in one consecutive series of Arabic numerals. Artwork for each figure should be provided in a separate file. Each figure should have an accompanying caption. Artwork should be submitted as TIFF or EPS format (1200 dpi for line and 300 dpi for half-tones and gray-scale art). Color art should be in the CMYK color space. Tables should be numbered and referred to by number in the text. Each table should be typed on a separate sheet of paper and should have a descriptive title. Center the title above the table, and type explanatory footnotes (indicated by superscript lowercase letters) below the table.

References

The accuracy of references is the responsibility of the contributing authors. The journal uses numeric referencing for references in text. The journal uses numeric listing of references in the order they were used in text (1, 2, 3, etc.) in the reference list. Use initials and surnames for all authors and list all authors for each publication up to six authors. Use et al. after the sixth author. The journal uses a specific style for reference in the reference list. Please see examples below and note that the appropriate journal title abbreviations can be found at the National Library of Medicine's List of Journals Indexed in Index Medicus. Please do consult a recent issue of the journal for sample references.

Examples:

1. Pfiffer LJ, McBurnett K (2006) Family correlates of comorbid anxiety disorders in children with attention-deficit/hyperactivity disorder. **J** Abnorm Child Psychol 34: 725-735
2. Negoro H, Sawada **M,** Iida T, Tanaka S, Kishimoto T (2010). Prefrontal dysfunction in attention- deficit/hyperactivity disorder as measured by near infrared spectroscopy. Child Psychiatry Hum Dev 41: 133-155
3. Muris P (2007) Normal and abnormal fear and anxiety in children and adolescents. Elsevier, Oxford, **UK**

Summary

The format for database articles in *Child Psychiatry & Human Development* is identical to that of other peer-reviewed science outlets (Abstract, Introduction, Methods, Discussion, and References) with the exception that each article in the journal concludes with a section labeled *Summary*. The Summary follows the discussion section and is basically an elaborated Abstract. Please consult back issues including those online at the journal portal at http://www.springer.com/10578 for additional guidance and examples.

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- No data have been fabricated or manipulated (including images)to support your conclusions
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To ensure objectivity and transparency in research and to ensure that accepted principles of ethical and professional conduct have been followed, authors should include information regarding sources of funding, potential conflicts of interest (financial or non-financial), informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals.

Authors should include the following statements (if applicable) in a separate section entitled "Compliance with Ethical Standards" before the References when submitting a paper:

- Disclosure of potential conflicts of interest
- Research involving Human Participants and/or Animals
- Informed consent

Please note that standards could vary slightly per journal dependent on their peer review policies (i.e. double blind peer review) as well as per journal subject discipline. Before submitting your article check the Instructions for Authors carefully. The corresponding author should be prepared to collect documentation of compliance with ethical standards and send if requested during peer review or after publication. The Editors reserve the right to reject manuscripts that do not comply with the above- mentioned guidelines. The author will be held responsible for false statements or failure to fulfill the above-mentioned guidelines.

Disclosure of potential conflicts of interest

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- Financial support for attending symposia
- Financial support for educational programs
- Employment or consultation
- Support from a project sponsor
- Position on advisory board or board of directors or other type of management relationships
- Multiple affiliations

- Financial relationships, for example equity ownership or investment interest
- Intellectual property rights (e.g. patents, copyrights and royalties from such rights)
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The corresponding author collects the conflict of interest disclosure forms from all authors. In author collaborations where formal agreements for representation allow it, it is sufficient for the corresponding author to sign the disclosure form on behalf of all authors. Examples of forms can be found

- here:

The corresponding author will include a summary statement, on the title page that is separate from their manuscript that reflects what is recorded in the potential conflict of interest disclosure form.

See below examples of disclosures:

Funding: This study was funded by X (grant number X).

Conflict of Interest: Author A has received research grants from Company A. Author B has received a speaker honorarium from Company X and owns stock in Company Y. Author C is a member of committee Z.

If no conflict exists, the authors should state:

Conflict of Interest: The authors declare that they have no conflict of interest.

Research involving human participants and/or animals

1) Statement of human rights

When reporting studies that involve human participants, authors should include a statement that the studies have been approved by the appropriate institutional and/or national research ethics committee and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. If doubt exists whether the research was conducted in accordance with the 1964 Helsinki Declaration or comparable standards, the authors must explain the reasons for their approach, and demonstrate that the independent ethics committee or institutional review board explicitly approved the doubtful aspects of the study.

The following statements should be included in the text before the References section:

Ethical approval: "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

For retrospective studies, please add the following sentence:

"For this type of study formal consent is not required."

Informed Consent

All individuals have individual rights that are not to be infringed. Individual participants in studies have, for example, the right to decide what happens to the (identifiable) personal data gathered, to what they have said during a study or an interview, as well as to any photograph that was taken. Hence it is important that all participants gave their informed consent in writing prior to inclusion in the study.

Identifying details (names, dates of birth, identity numbers and other information) of the participants that were studied should not be published in written descriptions, photographs, and genetic profiles unless the information is essential for scientific purposes

and the participant (or parent or guardian if the participant is incapable) gave written informed consent for publication. Complete anonymity is difficult to achieve in some cases, and informed consent should be obtained if there is any doubt. For example, masking the eye region in photographs of participants is inadequate protection of anonymity. If identifying characteristics are altered to protect anonymity, such as in genetic profiles, authors should provide assurance that alterations do not distort scientific meaning.

The following statement should be included:

Informed consent: informed consent was obtained from all individual participants included in the study."

If identifying information about participants is available in the article, the following statement should be included:

Additional informed consent was obtained from all individual participants for whom identifying information is included in this article."

Editorial Procedure

This journal follows a single-blind reviewing procedure.

APPENDIX 1: DATA EXTRACTION TOOL

Pharmacological Management of Core Symptoms and Comorbidities of Autism Spectrum Disorder in Children and Adolescents: A Systematic Review

Therapeutic Agent and Study Reference	Sample Size	Country	Comorbidities of ASD Domains		Core Symptoms of ASD Domains	
			Comorbidity	Results and Management Effectiveness	Improved Outcome Measure for Core Symptoms	Results and Management Effectiveness

APPENDIX 2: SEARCH STRATEGY

Pharmacological Management of Core Symptoms and Comorbidities of Autism Spectrum Disorder in Children and Adolescents: A Systematic Review

Proposed search strategy for PubMed

1. Pharmacological OR "Drug Therapy"[Mesh] OR Drug OR Pharmacotherapy
2. Treatment OR Treatments OR Management
3. Autism OR "Autism Spectrum Disorder"[Mesh] OR ASD
4. "Comorbidity"[Mesh]
5. “Core Symptom” OR “Core Symptoms”
6. Children OR "Child"[Mesh] OR Adolescent
7. #1 AND #2 AND #3 AND #6
8. #7 AND #4
9. #7 AND #5

Search Strategy for Scopus, Science Direct and PsycInfo

1. Pharmacological OR Drug OR “Drug Therapy” OR Pharmacotherapy
2. Treatment OR Treatments OR Management
3. Autism OR Autism Spectrum Disorder OR ASD
4. Children OR Child OR Adolescent
5. Comorbidity
6. “Core Symptoms”

Appendix 3, Quality Appraisal of Studies Utilizing the JBI Critical Appraisal Checklist for Randomized Control Trials [1]

Pharmacological Management of Core Symptoms and Comorbidities of Autism Spectrum Disorder in Children and Adolescents: A Systematic Review

Reviewers: Jennal Maniram and Ebenezer Wiafe

Date: 7-02-2022

Study Year and Author Citation : 2017 [2]

Record No: 1

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	☐	☐	✓	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score – 92%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2017 [3]

Record No: 2

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	✓	☐	☐	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score – 100%

Comments (Including reason for exclusion

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2019 [4]

Record No: 3

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	✓	☐	☐	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score – 100%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2015 [5]

Record No: 4

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	☐	☐	✓	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score – 92%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2018 [6]

Record No: 5

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	☐	☐	✓	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score – 92%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2017 [7]

Record No: 6

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	☐	☐	✓	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score – 92%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2019 [8]

Record No: 7

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	☐	☐	✓	☐
5. Were those delivering treatment blind to treatment assignment?	☐	☐	✓	☐
6. Were outcomes assessors blind to treatment assignment?	☐	☐	✓	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score – 77%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2016 [9]

Record No: 8

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	✓	☐	☐	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score –100%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2017 [10]

Record No: 9

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	✓	☐	☐	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score –100%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2018 [11]

Record No: 10

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	☐	☐	✓	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score –92%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2019 [12]

Record No: 11

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	✓	☐	☐	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score –100%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2021 [13]

Record No: 12

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	✓	☐	☐	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score –100%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2016 [14]

Record No: 13

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	☐	☐	✓	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	✓	☐	☐	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score –92%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2015 [15]

Record No: 14

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	✓	☐	☐	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score –100%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2016 [16]

Record No: 15

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	✓	☐	☐	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score –100%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2021 [17]

Record No: 16

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	✓	☐	☐	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score –100%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2020 [18]

Record No: 17

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	☐	☐	✓	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score –92%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2018 [19]

Record No: 18

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	✓	☐	☐	☐
7. Were treatment groups treated identically other than the intervention of interest?	☐	☐	✓	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score –92%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2021 [20]

Record No: 19

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	✓	☐	☐	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score – 100%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2017 [21]

Record No: 20

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	☐	☐	✓	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	☐	☐	✓	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score – 83%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2020 [22]

Record No: 21

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	☐	☐	✓	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	✓	☐	☐	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score – 92%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2019 [23]

Record No: 22

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	✓	☐	☐	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score – 100%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2018 [24]

Record No: 23

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	☐	☐	✓	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	✓	☐	☐	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score – 92%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2018 [25]

Record No: 24

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	☐	☐	✓	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score – 92%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2021 [26]

Record No: 25

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	✓	☐	☐	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score – 100%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2017 [27]

Record No: 26

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	☐	☐	✓	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	☐	☐	✓	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score – 83%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2019 [28]

Record No: 27

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	✓	☐	☐	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score -100%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2019 [29]

Record No: 28

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	☐	☐	✓	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score - 92%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2013 [30]

Record No: 29

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	✓	☐	☐	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score – 100%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2012 [31]

Record No: 30

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	✓	☐	☐	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score – 100%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2012 [32]

Record No: 31

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	✓	☐	☐	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score – 100%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2013 [33]

Record No: 32

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	☐	☐	✓	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score – 92%

Comments (Including reason for exclusion)

Reviewers: Jennal Maniram and Ebenezer Wiafe Date: 7-02-2022

Study Year and Author Citation: 2013 [34]

Record No: 33

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	✓	☐	☐	☐
2. Was allocation to treatment groups concealed?	✓	☐	☐	☐
3. Were treatment groups similar at the baseline?	✓	☐	☐	☐
4. Were participants blind to treatment assignment?	✓	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	✓	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	✓	☐	☐	☐
7. Were treatment groups treated identically other than the intervention of interest?	✓	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	✓	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	✓	☐	☐	☐
11. Were outcomes measured in a reliable way?	✓	☐	☐	☐
12. Was appropriate statistical analysis used?	✓	☐	☐	☐
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?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐ Appraisal Score – 100%

Comments (Including reason for exclusion)

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Appendix 4 - PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 26
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 26 - 27
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 28
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 29
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 29
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 30
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 30 & 31
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Appendix 1 and Pages 30 - 33
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 20 and Figure 1
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	N/A
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 30 -31 and Appendix 3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	N/A
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Appendix 1
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 31

Section and Topic	Item #	Checklist item	Location where item is reported
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1, Page 33
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1, Page 33
Study characteristics	17	Cite each included study and present its characteristics.	Table 1 (Page 32 -39) and Table 2 (Page 42 -47)
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Appendix 3 and Page 32
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 1 (Page 32 -39) and Table 2 (Page 42 -47)
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 31
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pages 52-54
	23b	Discuss any limitations of the evidence included in the review.	Page 54
	23c	Discuss any limitations of the review processes used.	Page 54
	23d	Discuss implications of the results for practice, policy, and future research.	Page 54
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 26

Section and Topic	Item #	Checklist item	Location where item is reported
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Pages 17 - 24
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Pages 54 - 55
Competing interests	26	Declare any competing interests of review authors.	Page 55
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 55

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71. doi: 10.1136/bmj. n71

For more information, visit: http://www.prisma-statement.org/

Appendix 5 - Data extraction tool for the retrospective patient file review at the public hospital

Patient No	Age	Gender	Name of medication/s prescribed	Dose and frequency of medication/s	Medical Comorbidity	Non-pharmacological interventions	Date of diagnosis	Prescribers notes relevant to therapeutic outcome.