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Global pharmaceutical care approaches to autism spectrum disorder: a scoping review protocol

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ABSTRACT

Objective: The aim of this review is to map the literary evidence on pharmaceutical care approaches and trends being seen globally for the treatment of the signs and symptoms of autism spectrum disorder (ASD).

Introduction: ASD is a neurodevelopmental condition synonymous with sliding-scale behavioral, communication, learning, and social problems. Causes include genetic and environmental factors. Pharmaceuticals are prescribed to treat the behavioral patterns of ASD.

Inclusion criteria: This review will incorporate studies that report on the pharmaceutical care approaches used to treat the signs and symptoms of ASD as well as to identify the global trends related to their use. Studies not falling under the ASD umbrella will be excluded. All primary, secondary, and gray literature will be included. No language restrictions will be applied. Studies from January 1, 1984, will be included.

Methods: This review will be conducted in line with the JBI methodology for scoping reviews and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews. A preliminary search of MEDLINE (PubMed) will be followed by searches of Emcare (Ovid), Nursing and Allied Health Premium (ProQuest), and Google Scholar. Two independent reviewers will screen titles and abstracts and extract data from selected sources. A third reviewer will adjudicate any conflicts until consensus is reached. The findings will be presented in a narrative summary with accompanying gap maps, figures, and tables.

Review registration: Open Science Framework https://osf.io/c234m

Keywords: autism; autism spectrum disorder; global distribution; pharmaceuticals

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Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that causes significant social, communication, learning, and behavioral difficulties.[1] Genetic and environmental risk factors are most associated with its occurrence.[2] Studies conducted on twins estimate the heritability of the disorder to be between 64% and 91%.[3,4] The broad agreement rate of ASD observable characteristics in monozygotic twins is 70% to 90% and 0% to 30% in dizygotic twins.[4,5]

The disorder manifests as a result of early altered brain development and neural reorganization.[6] The impact of these alterations and the ensuing dysregulation in neuronal circuits and synaptic functions remains misunderstood.[3] Neuroimaging studies have identified the prevalence of abnormal trajectories of brain development as the probable cause of autism, as opposed to localized lesions or static changes.[2] These studies also revealed a disruption in the balancing act required between cellular and synaptic growth and the precise timing of synaptic and neuronal pruning necessary for successful brain development. Bijl *et al.*[7] and Gabriele *et al.*[8] discovered that some people with ASD and their first-degree relatives exhibited elevated levels of platelet serotonin; however the basis for this biomarker remains unclear.

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ASD can be a lifelong disability and typically appears before the age of 3 years. Some children begin showing signs of the disorder by the time they are 12 months old.[1] Individuals with ASD often have no physical differences from neurotypical individuals and can usually continue living an unaltered life, communicating and learning at a comparatively equivalent or advanced level. However, other individuals with autism may present as non-verbal and require assistance with everyday tasks.[1]

While a variety of signs and symptoms may be present, 2 are prevalent across the spectrum and have become synonymous with the disorder: i) issues related to social communication and interaction skills, and ii) restricted, repetitive sensory-motor behaviors.[6] As a result of their broad prevalence, and because of the lack of reliable neurological biomarkers associated with the disorder, the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5) report of 2013 set these factors as the main diagnostic characteristics for the disorder.[6,9] This allows subtypes such as pervasive development disorder or Asperger's syndrome to be consolidated under the ASD banner.[6]

A 2022 review by Zeidan *et al.*[10] examining the global prevalence of ASD across different regions of the world concluded that 1 in 100 children are diagnosed with ASD. It reported that there has been a significant increase in prevalence since 2012 and attributed this to multiple factors, including the progress made in identifying cases and more adequately defining the disorder; an increase in community awareness and global public health responses;[10] and the development of more sophisticated diagnostic instruments, which have helped improve the accuracy of diagnosis.[3] Challenges included the significant variability of the prevalence of ASD estimates across geographic regions, with estimates in African and Eastern European regions being limited or non-existent.[10]

The heterogenicity of the etiology surrounding ASD has contributed to the stasis in the development of effective pharmacological treatments for the core condition.[11] Psychotropic medication has become most widely used in the treatment of the signs and symptoms and is prescribed to roughly two-thirds of adolescent individuals with the disorder.[11] Underlying comorbidities have made it common for individuals with autism to be prescribed additional medication as part of their treatment regimens.[12] The rates of polypharmacy range from 12% to 35%.[13] Some researchers have attributed this to the growing knowledge of the interplay between ASD and other mental health issues,[14] while others have pointed to medical aid access, geography, or race playing a more crucial role in the observation.[15]

Serotoninergic medications, such as selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs), are used to regulate the amount of serotonin in the brain by inhibiting serotonin reuptake from the synaptic cleft, thus stimulating neurogenesis and neuroprotection.[11] Irritability and repetitive behaviors are treated using atypical antipsychotics,[16,17] sleep issues are addressed with melatonin,[18] and stimulant medications or alpha-2-adrenergic agonists are used to treat coexisting attention deficit and hyperactivity disorder (ADHD).[16,18] N-acetylcysteine regulates the excitation–inhibition ratio associated with some subsets of ASD.[19] Dietary supplements such as sulforaphane[20–22] (an antioxidant, anti-inflammatory, and mitochondrial protective agent[23]) and omega-3 fatty antioxidants[24,25] have also been proposed as pharmaceutical options. Oxytocin, bumetanide, metformin, lovastatin, cannabidiol, arbaclofen, trofinetide, phosphodiesterase 4D inhibitors, and anavex 2-73 are new treatments needing further investigation.

A scoping review is best suited to mapping the available literature on a topic as wide-ranging as the multitude of pharmaceutical products being prescribed to treat the signs and symptoms of ASD around the world.[26] A scoping review format is justified, as pharmaceutical care approaches for ASD vary widely, determined by the focus of treatment to address the many different signs and symptoms related to the spectrum of this disorder.[11] Preliminary search results suggest a paucity of research information will be found regarding pharmaceutical care approaches to ASD in some global regions. Hence, research gaps may be identified in relation to global pharmaceutical distribution trends.

The results of this review will illuminate the global pharmaceutical approaches to the signs and symptoms of ASD; reveal whether worldwide consensus or trends exist regarding the preferred use of certain drugs; and show variations in usage, possibly due to the availability and distribution of some drugs. A preliminary search of MEDLINE (PubMed), the Cochrane Database of Systematic Reviews, and *JBI Evidence Synthesis* was conducted in September

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2023 and found no current or in-progress scoping reviews on the topic.

Review questions

i) What are the pharmaceutical care approaches (including the geographical distribution of such approaches) to the treatment of the signs and symptoms of ASD?
ii) What are the global trends in the pharmaceutical care approaches to the treatment of the signs and symptoms of ASD?

Inclusion criteria

Participants

This review will incorporate studies reporting on children or adults diagnosed with ASD who have used pharmaceuticals to treat their signs and symptoms. Studies focusing on the pharmaceutical treatment of individuals with a neurodevelopmental disorder not fitting under the ASD umbrella will be excluded. In mixed population studies, the focus will be on the use of the pharmaceutical products (perhaps initially developed for treatment of a comorbid condition) to treat the signs and symptoms of ASD. Only data pertaining to the use of the pharmaceutical product to treat the signs and symptoms of ASD specifically will be included in this review.

Concept

There will be 2 concepts of interest for the review. The first will be the identification of pharmaceutical treatment options currently being used. In this regard, the occurrence of mono- or polypharmacy, the dosage of the treatment option, the duration of the intervention, and the age group of the participants in trial studies, among other factors, will be included when available and pertaining to the treatment of the signs and symptoms of ASD. The second concept will be the identification of global trends in the usage of pharmaceutical products to treat the signs and symptoms of ASD. This will be achieved based on the calculation of frequency according to location.

If a study describes the use of a pharmaceutical for the treatment of the signs and symptoms of ASD that was developed initially for the treatment of another neurodevelopmental disorder, such as epilepsy, bipolar disorder, or ADHD, it will be considered for inclusion providing its use in the study is to treat the signs and symptoms of ASD exclusively.

Context

The focus of this scoping review will be on how pharmaceutical treatment of the signs and symptoms of ASD is carried out on a global scale. The global context is being used to detect whether there are any trends regarding pharmaceuticals used in certain countries and on certain continents. If a study reports on pharmaceutical, behavioral, or other treatments for the signs and symptoms of ASD being used in conjunction with each other, but there is no clear way to discern how the pharmaceutical treatment alone is used, the study will not be included.

Types of sources

This review will consider a hierarchy of evidence, ranging from meta-analyses, systematic reviews, and randomized controlled trials as the most rigorous evidence, to mid-level descriptive observational study designs and descriptive cross-sectional studies, and, finally, case reports, case studies, and expert opinion at the lower end of the scale. As this is a scoping review, information contained in dissertations, theses, conference abstracts, and gray literature sourced from the web on the study topic will also be considered for inclusion. The review will consider qualitative evidence collected using recognized qualitative methods as well as text and opinion pieces relating experiences with the pharmaceuticals used to treat the signs and symptoms of ASD.

Methods

The proposed review will follow the JBI methodology for scoping reviews,[27] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR).[28]

Search strategy

The search strategy will be designed to find both published and unpublished papers. A preliminary search was conducted of MEDLINE (PubMed) to identify articles on the study topic. The following keywords and terms were used: "autism," "autism spectrum disorder," "autistic spectrum disorder," "ASD," "pharmaceutical," "medicine," "drug," "treatment," "approach," "acetylcysteine," "arbaclofen," "aripiprazole," "atomoxetine," "amino butyric acid," "buspirone," "cannabis," "cannabinoids," "cannabidiol," "clonidine," "clozapine," "glutamatergic

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agents," "guanfacine," "lithium," "melatonin," "oxytocin," "prednisolone," "pregnenolone," "risperidone," and "vasopressin" (see Appendix I). Keywords, index terms, and MeSH terms found using the first search by analyzing the titles and abstracts of the articles[29] will then be used in a second systematic search that will include gray literature. At this stage, searches will be conducted in Embase, Emcare (Ovid), Nursing and Allied Health Premium (ProQuest), Scopus, and Google Scholar, making sure to adapt the index terms, MeSH terms, and keywords to suit the search format in each one. Results from Google Scholar will be considered by their relevance to the research questions up to the first 20 pages. The reference lists of the included sources will be screened for additional studies. A librarian will be consulted at this stage of the search to ensure that all relevant literature has been sourced using the chosen search terms.

The search will include abstracts, full texts, books, and documents. No limitations regarding language will be applied. Studies in languages other than English that can be translated using Google Translate to a point where information relevant to the review can be extracted will be included.

Studies from January 1, 1984, to the present will be considered for inclusion. This is because the overall number of papers retrieved on the research topic indicated a general increase from 1984, even though some years showed a reduction in the number of sourced papers. Reviews included in the 1980s time frame will also include earlier literature, which guided the decision to consider such a wide-ranging chronological timeframe (see Figure 1).

Study selection

After the search, all the identified citations will be combined and uploaded into EndNote v.21 (Clarivate Analytics, PA, USA), and duplicates will be removed. A pilot screening using a small sample of studies will be undertaken beforehand by the entire team using the inclusion criteria until 75% (or greater) agreement is reached on eligibility. Titles and abstracts will then be screened by 2 independent reviewers (RMS and DAS) against the inclusion criteria. Sources that are found to be relevant to the study topic will be retrieved in full and imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI; JBI, Adelaide, Australia).[30]

The full-text literature will be further assessed against the inclusion criteria by the same 2 independent reviewers (RMS and DAS). The removal of any literature at this stage that does not meet the inclusion criteria will be reported in the final scoping review with reasons. Conflicts of opinion that arise between the reviewers at any stage of the selection process will be dealt with by discussion or with an additional independent reviewer (BM). Relevant additional articles found through the perusal of the reference lists of the included articles will also be uploaded. All relevant findings will be reported in the scoping review and presented in a PRISMA flow diagram.[31]

In order to prevent duplication of included studies, identification of relevant primary studies reported in included reviews will be undertaken. Then, primary studies and gray literature not mentioned in the reviews but sourced in the search strategy process will also be considered to ensure all relevant information is included.

Data extraction

Two independent reviewers (RMS and DAS) will extract data using a data extraction tool (see Appendix II). A third independent reviewer (BM) will assess the efficacy of the predefined data extraction instrument in a pilot screening using a small sample of studies beforehand to ensure that all appropriate data are captured. The extracted data will contain specific details about the participants of any age in the studies, concept, context, study methods, and key findings relevant to the review questions.

The data extraction tool will be modified and revised, if necessary, in conjunction with ongoing feedback regarding the efficacy of the tool. Any modifications will be detailed in the review. To ensure all relevant data are collected, a maximum of 3 attempts will be made to contact the authors of papers to ask for missing or additional data, if required.

Data analysis and presentation

Text data will be progressively charted according to its relevance to ensure easier collation of data after extraction is completed. A descriptive analysis of the extracted information will be presented as tables, frequency counts, map charts, and diagrams to provide a visual representation of the strategy and selection process. Tables will be described further in narrative summaries.

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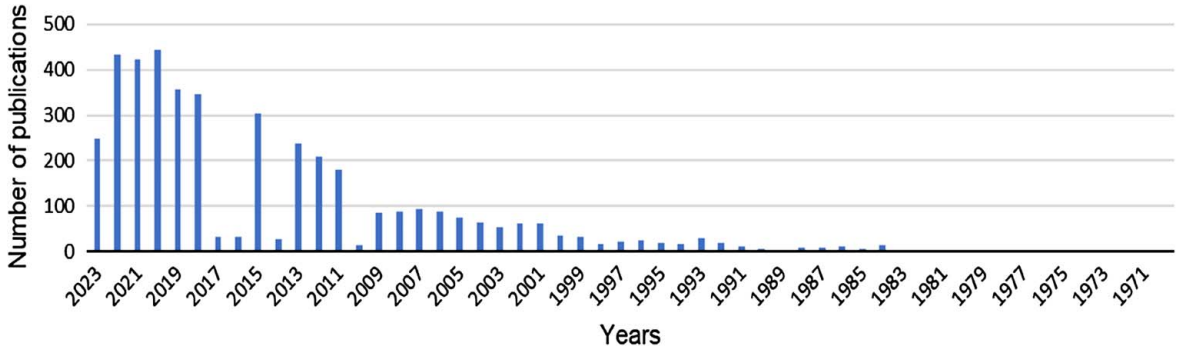

Figure 1: Number of publications on global pharmaceutical care approaches to autism spectrum disorder by year

Gap maps will be used to show the global trends in pharmaceutical care approaches to ASD and highlight gaps in the literature. The research questions of this review cover a broad spectrum of evidence on the topic and it is likely that many relevant studies will be found, hence the use of evidence and gap maps (EGMs) incorporating a primary framework of columns and rows. Additional secondary filtering options will be used for focused exploration of the map. This enhanced visual display and the ability to hone in on any particular sector or sub-sector will allow a better understanding of the findings.[32] In particular, in answering the research questions, a systematic presentation will be articulated using the EGMs of the different pharmaceutical care approaches available, the geographical distribution of these approaches, and the global trends related to such pharmaceutical interventions. With regard to the latter, evidence of mono- or polypharmacy will also be included.

Both quantitative and qualitative data can be presented using the tools listed above. Mono- and polypharmacy will be tabulated according to factors such as their use, location, and age group, as reported in the included sources. Figures such as map charts will be used to further present the global trends identified. However, qualitative data will be categorized using basic data coding and reported according to the themes presented in the literature.

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Appendix I: Search strategy

MEDLINE (PubMed)
Search conducted on November 18, 2023

Search: (((((((autism[Text Word]) OR (autism spectrum disorder[Text Word])) OR (autistic spectrum disorder[Text Word])) OR (ASD[Text Word])) OR (autism[MeSH Terms])) OR (autism spectrum disorder[MeSH Terms])) OR (autistic disorder[MeSH Terms])) AND ((((((((((((((((((((((((pharmaceutical[Text Word])) OR (medication[Text Word])) OR (drug[Text Word])) OR (acetylcysteine[Text Word])) OR (arbaclofen[Text Word])) OR (aripiprazole[Text Word])) OR (atomoxetine[Text Word])) OR (amino butyric acid[Text Word])) OR (buspirone[Text Word])) OR (cannabis[Text Word])) OR (cannabinoid[Text Word])) OR (cannabidiol[Text Word])) OR (cilostazol[Text Word])) OR (clonidine[Text Word])) OR (clozapine[Text Word])) OR (glutamatergic agents[Text Word])) OR (guanfacine[Text Word])) OR (lithium[Text Word])) OR (melatonin[Text Word])) OR (oxytocin[Text Word])) OR (prednisolone[Text Word])) OR (pregnenolone[Text Word])) OR (risperidone[Text Word])) OR (vasopressin[Text Word])))

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Appendix II: Draft data extraction instrument

Author, year	
Study design	
Origin (country, setting)	
Aim/purpose	
Study method	
Population and sample size (age group, total number)	
Target signs and symptoms of ASD	
Intervention(s) and duration of intervention(s)	
Key findings	

ASD, autism spectrum disorder.

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