GAJKIEWICZ, Magdalena, ZAUCHA, Radosław, SILLDORFF, Julia, FURA, Tomasz, ZAJĄC, Małgorzata, DUDEK, Marcin, FELIŃSKA, Zuzanna, ISZCZUK, Oliwia and ANCZYK, Stanisław. Propranolol in treating various symptoms associated with autism spectrum disorder (ASD). Quality in Sport. 2024;19:53778. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.19.53778
https://apcz.umk.pl/QS/article/view/53778

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 23.07.2024. Revised: 06.08.2024. Accepted: 12.08.2024. Published: 17.08.2024.

Propranolol in treating various symptoms associated with autism spectrum disorder (ASD)

Magdalena Gajkiewicz

Provincial Specialist Hospital No. 5, St. Barbara in Sosnowiec, Poland

https://orcid.org/0009-0000-0295-3591

Radosław Zaucha

Edward Szczeklik Specialist Hospital in Tarnów, Poland

https://orcid.org/0009-0001-6328-6443

Julia Silldorff

Provincial Specialist Hospital No. 5, St. Barbara in Sosnowiec, Poland

https://orcid.org/0009-0002-9223-2089

Tomasz Fura

Provincial Specialist Hospital No. 5, St. Barbara in Sosnowiec, Poland

https://orcid.org/0009-0008-0947-8058

Małgorzata Zając

St Maximilian District Hospital in Oświęcim

https://orcid.org/0009-0003-3870-2382

Marcin Dudek

Provincial Specialist Hospital No. 5, St. Barbara in Sosnowiec, Poland
https://orcid.org/0009-0003-6762-0124
Zuzanna Felińska
Provincial Specialist Hospital No. 5, St. Barbara in Sosnowiec, Poland
https://orcid.org/0009-0001-6717-5644
Oliwia Iszczuk
District Complex of Health Care Facilities in Będzin
https://orcid.org/0009-0002-0478-9582
Stanisław Anczyk
SKN przy Katedrze i Klinice Dermatologii WNMK SUM / Students' Research Group of the Department of Dermatology, Medical University of Silesia
https://orcid.org/0009-0006-8424-2147

Abstract

Introduction and purpose

This review provides an in-depth exploration of the pharmacology of propranolol, elucidating its mechanisms of action and clinical implications beyond its conventional indications, contextualizing propranolol's role in ASD management.

State of knowledge

Propranolol is a non-cardioselective β-adrenergic receptor antagonist, commonly used among the population. Propranolol's mechanisms include reducing cardiac workload, vasoconstriction, and membrane stabilizing properties, which suggest its utility in managing anxiety. ASD, characterized by deficits in social interaction, communication, and repetitive behaviors, affects approximately 1 in 100 children globally. Symptoms often co-occur with anxiety and hyperarousal, linked to noradrenergic system alterations.

Review methods

Electronic searches were conducted between 6 and 13 May 2024 and included databases: Pubmed and Google Scholar. This review focuses on 4 trials that are limited to years 2016-2024.

Conclusions

Overall, propranolol shows promise in managing anxiety, enhancing social communication, improving cognitive performance, and addressing severe behavioral challenges in ASD.

However, variability in response highlights the need for personalized treatment approaches. Further research is warranted to optimize dosing strategies and understand propranolol's mechanisms, contributing to more effective and tailored treatment options for ASD.

Keywords: autism, propranolol, b-blockers, anxiety

1. Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by challenges in social interaction, communication, and the presence of repetitive behaviors. Affecting approximately 1 in 100 children globally, ASD displays significant phenotypic variability and high heritability, though its precise etiology remains elusive. Symptoms of ASD, which typically become apparent by age three, can severely impact socialization, communication, and behavior, leading to substantial impairment in daily functioning.

Propranolol, a non-cardioselective β-adrenergic receptor antagonist, has been widely used for various medical conditions including hypertension, cardiac arrhythmias, and anxiety disorders. By blocking β1- and β2-adrenergic receptors, propranolol reduces cardiac workload and has the ability to penetrate the blood-brain barrier, making it a potential candidate for addressing the autonomic dysregulation often seen in ASD. Despite its off-label use for situational anxiety and performance anxiety, propranolol has not yet been officially indicated for the treatment of ASD.

Recent research has explored propranolol's effects on symptoms associated with ASD, such as anxiety, hyperarousal, and deficits in social communication. This review synthesizes findings from several clinical trials conducted between 2016 and 2024 to evaluate the efficacy and safety of propranolol in individuals with ASD. The following sections detail the methodology and summarize the outcomes of these studies, ultimately providing insights into the potential role of propranolol as an adjunct treatment for ASD.

2. State of knowledge

2.1 Propranolol

Propranolol, classified as a non cardioselective β-adrenergic receptor antagonist, functions by inhibiting the action of epinephrine and norepinephrine at both β1- and β2-adrenergic receptors [1].

Activation of beta-1 receptors, found on cardiac myocytes initiates an elevation in cyclic AMP levels, subsequently increasing intracellular calcium concentrations. This cascade augments muscle fiber contractility, consequently increasing the workload of the heart. Conversely, blockade of beta-1-adrenergic receptors induces a reduction in cardiac workload, thereby decreasing oxygen demand and eliciting myocardial remodeling.

Activation of beta-2 receptors, which are present in airway smooth muscles, triggers an increase in cyclic AMP, activating protein kinase A, which in turn induces the relaxation of smooth muscle cells in various organs and vessels. Consequently, blockade of beta-2 receptors results in mild vasoconstriction [2].

Both enantiomers of propranolol possess topical anesthetic effects, primarily mediated by the blockade of voltage-gated sodium channels. Experimental studies have elucidated propranolol's ability to block cardiac, neuronal, and skeletal voltage-gated sodium channels, contributing to its membrane stabilizing properties and manifesting as antiarrhythmic and other central nervous system effects [3]. Given its high lipophilicity, propranolol demonstrates the capability to penetrate the blood-brain barrier, suggesting its potential utility in managing anxiety disorders. For many years, beta blockers like propranolol have been utilized in the treatment of situational anxiety, including stage fright and exam- or interview-related anxiety [4].

Propranolol hydrochloride finds clinical use in the management of diverse medical conditions such as hypertension, pheochromocytoma, myocardial infarction, cardiac arrhythmias, angina pectoris, and hypertrophic cardiomyopathy. Additionally, it serves to alleviate symptoms associated with sympathetic overactivity in hyperthyroidism, anxiety disorders, and tremor. Further indications encompass the prophylaxis of migraine headaches and prevention of upper gastrointestinal bleeding in individuals with portal hypertension [1].

2.2 Autism disorder

Autism spectrum disorder (ASD), classified as a neurodevelopmental disorder within the pervasive developmental disorders category, is characterized by profound and pervasive deficits in reciprocal social interaction, qualitative impairments in communication, and repetitive or unusual behaviors [5]. It is estimated that approximately 1 in 100 children worldwide are diagnosed with autism spectrum disorder [6]. As a biologically based neurodevelopmental disorder, autism exhibits a high heritability rate, yet the precise etiology remains elusive. The complexity of genetics and phenotypic variability has presented challenges in identifying the exact cause. Autism is recognized as a multifaceted heritable condition involving multiple genes and displaying significant phenotypic diversity [7].

Symptoms of autism spectrum disorders primarily impact areas of socialization, communication, and behavior. While clinical indicators typically manifest by the age of three, delays in language development may impede early identification of symptoms [5].

Signs of autism spectrum disorder include deficits in social communication and interaction, as well as restricted, repetitive behaviors. These include challenges in social-emotional reciprocity, nonverbal communication, and relationship development. Additionally, individuals may display repetitive movements or speech, insistence on sameness, fixated interests, and sensory sensitivities. These signs contribute to the diagnostic criteria for ASD, varying in severity among individuals [8].

2.3 Influence of propranolol on people with ASD

Autism spectrum disorder (ASD) commonly co-occurs with symptoms of anxiety and hyperarousal. Although the precise alterations in the noradrenergic system in ASD remain incompletely understood, numerous functional indicators of the sympathetic/parasympathetic balance exhibit variations among individuals with ASD, often displaying considerable inter-individual variability.

Norepinephrine plays a pivotal role in the regulation of arousal. The locus coeruleus harbors the majority of noradrenergic neurons within the central nervous system and projects extensive efferents throughout the brain. In primates, the prefrontal cortex, implicated in various aspects of cognitive flexibility, projects afferents to the locus coeruleus [9]. Several studies have reported findings suggestive of heightened noradrenergic activity in ASD, including elevated plasma levels of epinephrine and norepinephrine [10], as well as alterations in the urinary excretion of various catecholaminergic metabolites [11].

Beta-adrenoceptor blocking medications, commonly known as beta blockers, act as competitive antagonists of noradrenaline and adrenaline at beta-adrenergic receptor sites. These receptors are distributed across both the peripheral and central nervous systems [12].

Propranolol has been utilized for several years as an off-label medication in the management of test anxiety [13] and performance anxiety [14].

Considering these factors, propranolol, as a beta blocker, may offer therapeutic advantages for individuals experiencing emotional, behavioral, and autonomic dysregulation associated with ASD. By targeting autonomic dysregulation and hyperarousal, propranolol has the potential to ameliorate symptoms and enhance therapeutic outcomes in individuals with ASD. Additionally, mitigating autonomic dysregulation and hyperarousal may contribute to the alleviation of emotional and behavioral challenges encountered by individuals with ASD [15].

3. Methods

Electronic searches were conducted between 6 and 13 May 2024 and included databases: Pubmed and Google Scholar. The following trials registers were searched using the search terms “propranolol OR beta blockers OR beta-adrenergic antagonists” AND “autism OR autism spectrum disorder OR ASD OR anxiety”. This review focuses on 4 trials that are limited to years 2016-2024.

In recent years, clinical trials have been conducted to investigate the potential influence of propranolol on individuals with autism spectrum disorder. However, despite these research efforts, it is notable that propranolol has not yet been granted an indication specifically for the treatment of ASD according to current prescribing guidelines and indications for the medication [16].

3.1 Effects of propranolol on conversational reciprocity in autism spectrum disorder: a pilot, double-blind, single-dose psychopharmacological challenge study

Twenty individuals diagnosed with high-functioning autism spectrum disorder (ASD) were recruited from the University of Missouri Thompson Center for Autism and Neurodevelopmental Disorders. Among them, 19 were male.

In a crossover design, each participant underwent two testing sessions. Baseline psychophysiological measurements were recorded at the beginning of each session. Participants received either 40 mg of propranolol or a placebo in a double-blinded, counterbalanced manner at the first session, with the opposite treatment at the second session. After a 60-minute waiting period to allow for peak drug effects, participants completed behavioral tasks and questionnaires, with continuous recording of psychophysiological measurements.

Conversational reciprocity was evaluated utilizing the Conversational Reciprocity task from the General Social Outcome Measure (GSOM CR), self-report anxiety was assessed via the Spence Children's Anxiety Scale (SCAS) and the Beck Anxiety Inventory (BAI), autonomic activity was assessed via psychophysiological measurements of electrocardiography (ECG) and skin conductance.

Propranolol significantly improved performance on the General Social Outcome Measure Conversational Reciprocity (GSOM CR) task total score compared to the placebo condition. However, the data for each domain of the task did not follow a normal distribution. Specifically, performance on the nonverbal communication domain scores improved with propranolol compared to placebo, although this finding did not withstand Bonferroni corrections for multiple comparisons. There was also a trend suggesting that propranolol improved sharing information scores. Task performance did not differ between propranolol and placebo for any other domain. Additionally, there were no significant differences in conversation length between drug conditions, and no observed order effects on task performance between the first and second study visits. Furthermore, Propranolol did not influence scores on the Beck Anxiety Inventory (BAI), according to a Wilcoxon signed-rank test [17].

3.2 Beta-adrenergic antagonism alters functional connectivity during associative processing in a preliminary study of individuals with and without autism

The study included 13 individuals diagnosed with autism spectrum disorder (ASD) and 13 matched typically developing (TD) controls, recruited from both a local neurodevelopmental disorder treatment and research center and the broader local community. Participants attended three sessions, where propranolol (40 mg), nadolol (50 mg), or placebo were orally administered in a blinded manner, with drug order counterbalanced across sessions and separated by at least 24 hours. Baseline autonomic nervous system measures, including heart rate (HR)/blood pressure (BP) and electrocardiogram (ECG), were recorded.

During functional magnetic resonance imaging, participants with and without ASD completed a semantic fluency task following drug administration. Autonomic nervous system measures and functional connectivity between language/associative processing regions and within specific networks (fronto-parietal control, dorsal attention, and default mode) were evaluated.

TD controls exhibited superior performance on the semantic fluency task compared to individuals with ASD, including higher average scores across all sessions, including placebo. It was noted that propranolol administration was linked to improved semantic fluency performance, correlated with baseline resting heart rate. Additionally, propranolol altered network efficiency in regions associated with semantic processing and reduced functional differences in the fronto-parietal control network in individuals with ASD, as observed in an exploratory analysis.

Furthermore, compared to placebo, propranolol administration was associated with decreased functional connectivity in the dorsal medial prefrontal cortex subnetwork of the default mode network and increased connectivity in the medial temporal lobe subnetwork, regardless of diagnosis. Functional connectivity is believed to play a role in autism spectrum disorder, with most research indicating reduced connectivity between distant brain regions alongside increased connectivity within specific local brain regions.

These effects were not observed with nadolol, as reported in a prior study by the same authors in 2016. This suggests that the changes in functional connectivity following propranolol administration were not solely attributable to peripheral cardiovascular effects [18].

3.3 Randomized controlled trial of propranolol on social communication and anxiety in children and young adults with autism spectrum disorder

A placebo-controlled trial employing double-blinding was conducted to assess the impact of the β-adrenergic antagonist propranolol on social interaction, anxiety, and language in individuals diagnosed with autism spectrum disorder (ASD). Enrollment comprised seventy-four participants aged between 7 and 24 years, who were randomly assigned to either the propranolol or placebo group for a duration of 12 weeks. Blinded assessments were administered at baseline, 6 weeks, and 12 weeks to evaluate the primary outcome measure, the General Social Outcome Measure-2 (GSOM-2), focusing on social interaction, and secondary outcomes, including the Clinician Global Clinical Impression-Improvement (CGI-I) ratings for social interaction, anxiety, and language.

Of the initial cohort, 69 participants successfully completed the 12-week assessment. The study outcomes revealed no statistically significant effects of propranolol on either the GSOM-2 or CGI-I ratings pertaining to social interaction and language. Nonetheless, noteworthy improvements were observed in the CGI-I ratings related to anxiety within the propranolol group at the conclusion of the 12-week period. Consistent with expectations, propranolol administration led to the anticipated reductions in heart rate and blood pressure, with adverse effects reported infrequently. Although propranolol did not demonstrate discernible effects on measures of social interaction or language, indications of its potential efficacy in managing anxiety among individuals with ASD were observed [19].

3.4 The Safety and Effectiveness of High-Dose Propranolol as a Treatment for Challenging Behaviors in Individuals With Autism Spectrum Disorders

A retrospective case series examined 46 individuals with autism spectrum disorder (ASD) displaying high levels of aggression, self-injurious, and disruptive behaviors treated with high-dose propranolol. The cohort included 8 females and 38 males, aged 8 to 32 years, all previously treated with at least one antipsychotic medication and most having received high-quality behavioral interventions.

Clinical information on challenging behaviors was gathered through meetings between the treating psychiatrist, patients, and caregivers. The severity of symptoms and medication efficacy were measured using the Clinical Global Impression (CGI) scales before and after propranolol treatment. The CGI-Severity (CGI-S) asks the clinician one question: “Considering your total clinical experience with this particular population, how mentally ill is

the patient at this time?". Initial doses started low (e.g., 10 mg, three times daily) and were increased as needed, with patients continuing their existing medications.

Results showed significant improvement in challenging behaviors for 85% of patients, slight improvement for 4%, and no improvement or worsening for 11%. Common symptoms like hyperactivity and repetitive behaviors did not show quantifiable improvement. Propranolol doses ranged from 120 to 960 mg per day, with treatment durations from 1 month to 10 years.

The study suggests high-dose propranolol can be effective for managing behavioral disorders in ASD, with a manageable safety profile under clinical supervision. However, the limited rigorous research and the heterogeneity of ASD indicate no single treatment is universally effective [20].

4. Summary and conclusions

The reviewed studies collectively highlight the potential utility of propranolol in treating various symptoms associated with autism spectrum disorder (ASD). A crossover, double-blind, single-dose trial involving 20 individuals with high-functioning ASD found that propranolol significantly improved conversational reciprocity, particularly nonverbal communication, although this did not withstand strict statistical corrections. There was no significant impact on anxiety or conversation length.

A three-session, crossover, double-blind study with propranolol (40 mg), nadolol (50 mg), or placebo, involving 13 individuals with ASD and 13 controls, found that propranolol improved semantic fluency and altered functional connectivity in brain regions associated with semantic processing. It reduced functional differences in the fronto-parietal control network in ASD and showed changes in connectivity within the default mode network, indicating central rather than peripheral effects.

A 12-week, double-blind, placebo-controlled trial with 74 participants demonstrated that propranolol significantly reduced anxiety but had no significant effects on social interaction or language. Expected reductions in heart rate and blood pressure were observed, with minimal adverse effects.

A retrospective case series of 46 individuals with ASD displaying high levels of aggression and disruptive behaviors found that high-dose propranolol significantly improved challenging behaviors in 85% of patients, with minimal effects on hyperactivity and repetitive behaviors. The safety profile was manageable under clinical supervision.

Overall, propranolol exhibits diverse benefits in managing anxiety, improving specific social communication skills, enhancing cognitive performance, and addressing severe behavioral challenges in individuals with ASD. However, the variability in response across different domains and individuals underscores the need for personalized approaches in clinical practice. These findings warrant further research to optimize propranolol dosing strategies and better understand its mechanisms of action in ASD, ultimately contributing to more effective and tailored treatment options for this heterogeneous disorder.

Disclosure

Author's contribution

Conceptualization: Magdalena Gajkiewicz and Radosław Zaucha; Methodology: Julia Silldorff; Software: Tomasz Fura; Check: Stanisław Anczyk and Marcin Dudek; Formal analysis: Zuzanna Felińska and Oliwia Iszczuk; Investigation: Tomasz Fura and Julia Silldorff; Resources: Małgorzata Zając; Data curation: Oliwia Iszczuk; Writing - rough preparation: Magdalena Gajkiewicz and Marcin Dudek; Writing - review and editing: Radosław Zaucha and Magdalena Gajkiewicz; Supervision: Stanisław Anczyk; Project administration: Małgorzata Zając and Zuzanna Felińska; Receiving funding - no specific funding.

All authors have read and agreed with the published version of the manuscript.

Financing statement

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflict of interest

The authors deny any conflict of interest.

References:

1) Al-Majed, A. A., Bakheit, A. H. H., Abdel Aziz, H. A., Alajmi, F. M., & AlRabiah, H. (2017). Propranolol. Profiles of Drug Substances, Excipients and Related Methodology, 287–338. doi:10.1016/bs.podrm.2017.02.006
2) Mahsa S, Vikas G. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. 2023 May 1.
3) Wang DW, Mistry AM, Kahlig KM, Kearney JA, Xiang J, George AL (2010). "Propranolol blocks cardiac and neuronal voltage-gated sodium channels". Frontiers in Pharmacology. 1: 144. doi:10.3389/fphar.2010.00144
4) Sagar-Ouriaghli I, Lievesley K, & Santosh P. J, (2018). Propranolol for treating emotional, behavioural, autonomic dysregulation in children and adolescents with autism spectrum disorders. Journal of Psychopharmacology, 32(6), 641–653. doi:10.1177/0269881118756245
5) Levy S. E, Mandell D. S, & Schultz R. T, (2009). Autism. The Lancet, 374(9701), 1627–1638. doi:10.1016/s0140-6736(09)61376-3
6) Zeidan J, Fombonne E, Scorah J eta al. (2022). Global prevalence of autism: A systematic review update. Autism Res. 15(5):778-790. doi: 10.1002/aur.2696
7) Johnson C. P, & Myers S. M, (2007). Identification and Evaluation of Children With Autism Spectrum Disorders. PEDIATRICS, 120(5), 1183–1215. doi:10.1542/peds.2007-2361
8) American Psychiatric Association. (2022). Diagnostic and statistical manual of mental disorders (5th ed., text rev.), p. 154-155

9) Beversdorf, D. Q. (2020). The role of the noradrenergic system in autism spectrum disorders, implications for treatment. Seminars in Pediatric Neurology, 100834. doi:10.1016/j.spen.2020.100834
10) Lake CR, Ziegler MG, Murphy DL. Increased norepinephrine levels and decreased dopamine-beta-hydroxylase activity in primary autism. Arch Gen Psychiatry 34:553–556; 1977.
11) Barthelemy C, Bruneau N, Cottet-Eymard JM, Domenech-Jouve J, Garreau B, Lelord G, Muh JP, Peyrin L. Urinary free and conjugated catecholamines and metabolites in autistic children.
12) Ward F, Tharian P, Roy M, Deb S, & Unwin G. L, (2013). Efficacy of beta blockers in the management of problem behaviours in people with intellectual disabilities: A systematic review. Research in Developmental Disabilities, 34(12), 4293–4303. doi:10.1016/j.ridd.2013.08.015
13) Faigel HC (1991) The effect of beta blockade on stress-induced cognitive dysfunction in adolescents. Clin Pediatr 30:441–445
14) Lader M (1988) β-adrenoceptor antagonists in neuropsychiatry: an update. J Clin Psychiatry 49:213–223
15) Sagar-Ouriaghli I, Lievesley K, & Santosh P. J, (2018). Propranolol for treating emotional, behavioural, autonomic dysregulation in children and adolescents with autism spectrum disorders. Journal of Psychopharmacology, 32(6), 641–653. doi:10.1177/0269881118756245
16) U.S. Food and Drug Administration. (2011). Propranolol Hydrochloride Tablets https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/016418s080,016762s017,017683s008lbl.pdf
17) Zamzow R. M, Ferguson B. J, Stichter J. P, Porges E. C, Ragsdale A. S, Lewis M. L, & Beversdorf D. Q (2016). Effects of propranolol on conversational reciprocity in autism spectrum disorder: a pilot, double-blind, single-dose psychopharmacological challenge study. Psychopharmacology, 233(7), 1171–1178. doi:10.1007/s00213-015-4199-0
18) Hegarty J. P, Zamzow R. M, Ferguson B. J, Christ S. E, Porges E. C, Johnson J. D, & Beversdorf D. Q. (2019). Beta-adrenergic antagonism alters functional connectivity during associative processing in a preliminary study of individuals with and without autism. Autism, 136236131986863. doi:10.1177/1362361319868633

19) David B, Bradley F, Samantha H, et al. (2024) Randomized controlled trial of propranolol on social communication and anxiety in children and young adults with autism spectrum disorder. Psychopharmacology; 241(1):19-32. doi: 10.1007/s00213-023-06452-1.

20) London E. B, Yoo J. H, Fethke E. D, & Zimmerman-Bier B, (2020). The Safety and Effectiveness of High-Dose Propranolol as a Treatment for Challenging Behaviors in Individuals With Autism Spectrum Disorders. Journal of Clinical Psychopharmacology, 40(2), 122–129. DOI: 10.1097/JCP.0000000000001175