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A Systematic Review of Therapeutic Interventions of Autistic Spectrum Disorders: Findings and Implications

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Table of Contents

List of Tables

Table of Figures

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Abstract

Introduction: Autism spectrum disorders (ASD) are an emerging health problem worldwide, particularly in Africa, but little is known about their pathogenesis. In addition, little is known about the burden of ASD in Africa, and there is currently no clear intervention nor policy guidelines to improve the lives of affected individuals. There is evidence in literature to support the on-going hypotheses of GABAergic abnormalities in ASD. Consequently, gamma-aminobutyric acid (GABA) modulators may be a potential treatment for people with ASD. However, this needs to be shown. **Objective:** Undertake a systematic review of recent studies and clinical trials of GABA modulators in ASD in order to guide research, interventions, and policy in Africa. **Results:** The findings from the systematic review support the studied drugs, particularly bumetanide, valproate, and acamprosate, as potentially effective and tolerable for individuals with ASD. However, there is limited evidence to support the use of these medicines for the treatment of the core symptoms of ASD. Consequently, additional studies concerning these medicines as a potential treatment are warranted. **Conclusion:** There appears to be a strong evidence-base that GABA modulators may be effective in the treatment of ASD. However, given current concerns, larger-scale randomized trials are needed in the near future to guide future guidelines and policies.

Key words: Autistic spectrum disorders, GABA, systematic review, clinical trials, Africa

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Abbreviations

ABC-C	Aberrant Behaviour Checklist-Community Edition
ABC-C_{FX}	Aberrant Behaviour Checklist-Community Edition, FXS-specific
ABC-H	Aberrant Behaviour Checklist-Hyperactivity
ABC-I	Aberrant Behaviour Checklist-Irritability
ABC-LSW	Aberrant Behaviour Checklist-Lethargy/Social Withdrawal
ABC-SA	Aberrant Behaviour Checklist-Social Avoidance
ADHD-RS	Attention Deficit Hyperactivity Disorder-Rating Scale
ADI	Autism Diagnostic Interview
ADOS	Autism Diagnosis Observation Schedule
ADOS-G	Autism Diagnosis Observation Schedule-Generic
ADI-R	Autistic Diagnostic Interview-Revised
ALS	Affective Liability Scale
AQ	Aggression Questionnaire
ASD	Autistic Spectrum Disorders
BIS-11	Barratt Impulsiveness Scale Version 11
CARS	Childhood Autism Rating Scale
CCT	Controlled Clinical Trial
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CSHQ	Children's Sleep Habits Questionnaire
CY-BOCS	Children's Yale-Brown Obsessive Compulsive Scale
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DSM-IV-R	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Revised
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision

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DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EEG	Electroencephalogram
EOWPVT	Expressive One-Word Picture Vocabulary Test
fMRI	Functional Magnetic Resonance Imaging
FXS	Fragile X Syndrome
Ham-D	Hamilton Depression Scale
GABA	Gamma-aminobutyric Acid
GAF	Global Assessment of Functioning Scale
GAS	Gilliam Autism Rating Scale
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
MOAS	Modified Overt Aggression Scale
PDD	Pervasive Developmental Disorders
PDD-NOS	Pervasive Developmental Disorder-Not Otherwise Specified
PEP-3	Psychoeducational Profile, 3rd Edition
PSI	Parenting Stress Index
RCT	Randomised Clinical Trial
RDEG	Regulation Disorder Evaluation Grid
ROWPVT	Receptive One-Word Picture Vocabulary Test
RRB	Repetitive and Restrictive Behaviour
SB-5	Stanford-Binet Intelligence Scales, 5th Edition
SED	Subclinical Epileptiform Discharge
SRS	Social Responsiveness Scale
VABS-II	Vineland Adaptive Behaviour Scale, 2nd Edition
VAS	Visual Analogue Scale
YBOCS	Yale Brown Obsessive Compulsion Scale

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Introduction

Autistic spectrum disorders (ASD) are an umbrella term that covers conditions such as autism, childhood disintegrate disorder, Asperger syndrome, Rett syndrome, and fragile X syndrome (FXS) (Fernandez and Scherer, 2017; Howes et al., 2018). ASD are also known as pervasive developmental disorders (PDD) because they involve delay in many areas of development. ASD are characterised by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V), as having impaired social and communication skills along with restricted and repetitive behaviours. At a global scale, the prevalence of ASD has increased appreciably over the past decade with recent estimates showing every 160 people has ASD with an estimated 7.6 million world-wide (Abubaker et al., 2016; World Health Organization, 2013). However, the prevalence of ASD remains unknown (National Academies of Sciences, Engineering, and Medicine, 2015; World Health Organization, 2013). The challenges being faced on the African continent include limited scientific research that could guide therapeutic interventions for some of the symptoms as there are concerns regarding pharmacological treatments for the core symptoms and lack of policies. As a result, factors such as poor diagnosis, management, and potential infectious aetiology continue to affect the management of ASD in Africa (Abubaker et al., 2016).

There is also currently limited data regarding the prevalence of ASD in Africa. Bakare and Munir reported the prevalence of ASD among sub-Saharan African children with intellectual disability to be approximately 0.7% more than 3 decades ago. Two studies disclosed a large significance of nonverbal ASD cases (51.2-71%) and over 60% comorbid intellectual disability among children with ASD (Belhadj et al., 2006; Mankoski et al., 2006). Fortunately, there is a growing interest in ASD in Africa with evidence of increased number of scientific studies on this complex disorder in the last decade (Abubaker et al., 2016; Ametepee and Chitiyo, 2009; Bakare and Munir, 2011). This is likely to grow with growing populations in Africa.

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Unfortunately, even today, an appreciable amount is not understood about ASD in Africa and its association of comorbid disorders, most of which are the cause of poor prognosis, morbidity and mortality among individuals with ASD (Mouridsen et al., 2008). Comorbid disorders, particularly epilepsy, have been well documented in children with ASD (Brondino et al., 2016; Frye et al., 2013). A recent study conducted in the Democratic Republic of Congo (DRC) reported 93% clinical cases of ASD having abnormal electroencephalogram (EEG) activities even in cases without comorbidities (Mpaka et al., 2016). Additionally, the frequency of epilepsy was 72.50% among 405 children and adolescents with ASD. Other reports have also documented a strong correlation between epilepsy and autism (Belhadj et al., 2006; Kim et al., 2006) and even theorized the involvement of epilepsy in the pathogenesis of autism (Mpaka et al., 2016).

Gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter of the CNS, targets two distinctive receptors: $GABA_A$ and $GABA_B$. Both receptors are broadly expressed in the CNS (Brondino et al., 2016). Interestingly, several studies have observed abnormalities in both $GABA_A$ and $GABA_B$ receptor subunits in the brains of autistic human subjects (Fatemi et al., 2010; Fatemi et al., 2014; Polan et al., 2014). Antiepileptic drugs, which comprise benzodiazepines, are therapeutically used for epilepsy, anxiety, and insomnia (Han et al., 2014). These drugs reduce anxiety and control seizures by binding to specific $GABA_A$ receptor subunits resulting in enhancement of GABAergic (inhibitory) transmission. Possibly in view of this, phenytoin (Bird, 2014), valproate (Hollander et al., 2006; 2010), clonazepam (Aman et al., 1995; Han et al., 2014), clobazam (Han et al., 2014; Leahy et al., 2011), carbamazepine (Aman et al., 1995; Martino and Tuchman, 2001), and levetiracetam (Rugino and Samsock, 2002) significantly attenuated autistic-like behaviours in patients at low doses.

However, antiepileptic drugs are not the only class of medicines reported to improve the core symptoms of ASD. Bumetanide, a diuretic indicated for oedema, has been shown to appreciably

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improve the core symptoms of autism in several reports (Bruining et al., 2015; Hadjikhani et al., 2015; Lemonnier and Ben-Ari, 2010; Lemonnier et al., 2012). It does so by decreasing chloride ions, and thus reinforcing GABAergic inhibition (Hadjikhani et al., 2015). Arbaclofen, a $GABA_B$ receptor agonist indicated for alcohol addiction, ameliorated autistic-like disorders in patients with FXS (Berry-Kravis et al., 2012). Additionally, supplementation with L-carnosine, a neuroprotective dipeptide and a player in the GABAergic system, also improved the core symptoms of autism in children in a double-blind, placebo-controlled study (Chez et al., 2002). What is encouraging is that all these treatments are GABA modulators. So far, however, the effect of GABA modulators has never been summarised.

Consequently, the objective of this systematic review is to determine the efficacy of GABA modulators in ASD. The aim is to review potential medical interventions of ASD that would significantly reduce disability-adjusted life years in Africa. As a result, seek to guide future scientific research, interventions, and policy on ASD in Africa.

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Methods

The systematic review of GABA modulators in ASD was undertaken according to the methodological guidelines of Cochrane systematic reviews. I wanted all selected articles to be from the 21st century. I searched the Cochrane Library, PubMed, Medline, CINAHL, and EMBASE citations from January, 2000 up to December, 2017 using the following key words: ("autism" OR "ASD") AND ("gaba"). All terms were searched individually and combined together. Terms for the following medicines were included: valproate, phenytoin, carbamazepine, clonazepam, clobazam, levetiracetam, bumetanide, arbaclofen, and acamprosate. L-carnosine, though a supplement, was also included due to its involvement in the GABAergic system.

The resulting articles were reviewed for further relevant references. Clinical trial registers were searched in order to find ongoing trials on the selected medications. I selected randomised (RCTs) and controlled clinical trials (CCTs), and open label trials, yielding primary results on the effects of the administration of GABA modulators in patients with ASD. ASD or PDD were characterised based on internationally valid diagnostic criteria such as the Autistic Diagnostic Interview-Revised (ADI-R) or the Diagnostic and Statistical Manual of Mental Disorders (DSM). The titles of all the studies located were assessed before reviewing and assessing the abstracts. I independently entered the data into Excel 2016 for Windows. The quality of the methodology was assessed using the Risk of Bias tool devised by Cochrane (Higgins and Green, 2011).

Data was displayed using a format which included study design, sample character, follow-up period, main findings, and adverse events. Eligibility for the study was based on the following inclusion criteria: (a) involved individuals of any age must be diagnosed with ASD, and (b) the studied drug must be a GABA modulator. Studies were excluded if they: (a) involved animal models which do not correspond to well-known clinical syndromes; (b) were case reports; (c) were abstracts, posters, or

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conference proceedings that were not published in a journal; (d) did not present innovative data (such as review articles or expert option); or (e) showed duplicate data. Although I considered conducting a meta-analysis on treatment outcomes, both study and clinical heterogeneities prevented a meta-analysis of any treatment outcome.

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Results

My search strategy yielded 590 citations. After screening of titles and abstracts, 559 were initially removed. Based on full-text examination of the papers, 16 articles were excluded, yielding 15 studies which fulfilled the inclusion criteria. The studies which fulfilled the inclusion criteria are summarised in Table 1. The quality of the included studies is characterised in Figures 1 and 2.

Four of the articles were studies comparing antiepileptic medications with placebo (Hollander et al., 2006, 2010; Rezaei et al., 2010; Wang et al., 2017), four studies of arbaclofen (Berry-Kravis et al., 2012, 2017; Erickson et al., 2013b; Veenstra-VanderWeele et al., 2016), four studies of bumetanide (Hadjikhani et al., 2015; Lemonnier and Ben-Ari, 2010; Lemonnier et al., 2012, 2017), two studies of carnosine (Chez et al., 2002; Hajizadeh-Zaker et al., 2017), and one study of acamprosate (Erickson et al., 2013a). Two studies evaluated carnosine (Hajizadeh-Zaker et al., 2017) and topiramate (Rezaei et al., 2010) in participants who were also administered risperidone during the trial period. Nine studies were conducted in the USA, three in France, two in Iran, one in Switzerland, and one in China. All were published in English. The mean duration of studies was 8.94 weeks (range = 1-24 weeks; standard deviation = 5.32). Sample sizes ranged from 5 to 278 participants. The mean age of the study population was 12.38 years. The overall reported proportion of diagnosis was as follows: FXS 50%, Autism 31%, Asperger syndrome 5%, and PDD 1%.

Arbaclofen significantly improved the Aberrant Behaviour Checklist (ABC)-Lethargy/Social Withdrawal scores in two studies (Berry-Kravis et al., 2012) but showed no significant difference from placebo on any subscale of the ABC and other measures including the Clinical Global Impression of Improvement (CGI-I) in two other studies (Berry-Kravis et al., 2017; Veenstra-VanderWeele et al., 2016). Chez et al. randomised 31 patients to L-carnosine or placebo. The dosage of carnosine was 400 mg twice daily. Among the patients, no significant differences were observed in the primary endpoints with exception for the communication subscale of the Gilliam Autism Rating

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Scale (GAS). Hajizadeh-Zaker et al. also investigated the safety and effectiveness of L-carnosine as add-on to risperidone in 42 children in a 10-week study. Risperidone was titrated up to 1 mg/day for children weighing less than 20 kg and 2 mg/day for children over 20 kg. Besides the inattention/hyperactivity subscale, no significant differences were observed in the other subscales.

Erickson et al. (2013a) conducted an open-label trial to investigate the safety and efficacy of acamprosate. Remarkably, significant improvements were observed in social behaviour (p=0.04) and inattention/hyperactivity (p=0.01). Hollander and colleagues evaluated the effectiveness and safety of valproate compared to placebo in two RCTs (Hollander et al., 2006, 2010). In the 2006 study, the primary endpoint was the Child Yale-Brown Obsessive Compulsive Scale (C-YBOCS). At the end of the 8-week trial, a significant group difference in C-YBOCS scores was noted such that repetitive behaviour scores improved on valproate and deteriorated on placebo (p=0.037). In the 2010 study, valproate significantly improved ABC-Irritability subscale scores in children and adolescents with ASD (p=0.048). Responder rate by CGI-I for irritability was significantly higher in valproate (p=0.008). However, there were no statistically significant differences in C-YBOCS (p=0.748).

Lemonnier and colleagues conducted one CCT and two RCTs with bumetanide (Lemonnier and Ben Ari, 2010; Lemonnier et al., 2012, 2017). Lemonnier and Ben-Ari tested bumetanide (1 mg/day) in 5 children with ASD in a 3-month open-label trial. Significant improvements of the scores of the Childhood Autism Rating Scale (CARS), the ABC, the Regulation Disorder Evaluation Grid (RDEG), and the Repetitive and Restricted Behaviour (RRB) were observed ((Lemonnier and Ben Ari, 2010). No adverse events were reported. However, no significant changes were noted in the CGI-I or Clinical Global Impression of Severity (CGI-S) score. Lemonnier et al. (2012) enrolled 60 children with ASD, 5 of which dropped out due to adverse events. Each patient was administered bumetanide 1 mg/day for 3 months. A significant improvement in the CARS score and in the CGI-I score was observed. The 2017 study enrolled 91 patients with ASD spanning the entire paediatric population (age range 2-18 years) and were subdivided in four age groups and randomised to receive bumetanide or placebo for 3

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months. Bumetanide significantly improved CGI (p=0.0043) and the Social Responsiveness Scale (SRS) by more than 10 points (p=0.02). The most common adverse event was hypokalemia, which was resolved after oral potassium supplementation. A low dose of bumetanide (1 mg twice daily) was considered favourable in improving the core symptoms of ASD without the adverse event.

Hadjikhani et al. conducted a 10-month open-label trial in which 7 male patients with ASD were administered bumetanide (1 mg/day). Significant improvements in face emotion recognition and in the total score of the Toronto Alexithymia Scale were noted. Moreover, functioning magnetic resonance imaging (fMRI) data showed an increased activation of brain regions involved in social and emotional perception during perception of emotional faces.

Wang et al. included 70 paediatric patients randomized to either levetiracetam or placebo. The average plasma concentrations of levetiracetam at 1 and 6 months was 30.9 and 34.4 μg/mL, respectively. The authors evaluated response using the Psychoeducational Profile, 3rd Edition (PEP-3), CARS and ABC. This study showed significant differences between the 2 treatment arms on the PEP-3 (p=0.005), CARS (p=0.031) and ABC scores (p=0.025). Rezaei et al. randomized 40 children with ASD to topiramate and placebo. All subjects were concurrently started on risperidone, which was titrated up to 2 mg/day for children weighing less than 40 kg and 3 mg/day for children over 40 kg. The primary endpoint was the ABC. The group treated with the combination of topiramate and risperidone showed significant improvements in ABC subscale scores, specifically irritability (p=0.04), stereotypes (p=0.04), and inattention/hyperactivity (p=0.04) compared to placebo group.

There are some ongoing clinical trials evaluating the efficacy of GABA modulators in ASD. These are summarized in Table 2. An open label trial (NCT00211796) has been designed to evaluate the potential beneficial effect of valproate on behaviour in participants with ASD but it is unknown whether the study has been completed or terminated. The other ongoing trials are randomised clinical trials. One study (NCT02278328) is recruiting male adolescents with ASD. The adolescents will be

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randomly assigned to arbaclofen or placebo for 4 weeks and will be evaluated using magnetoencephalography. All the trials are being conducted in the USA. No open-label or clinical trials evaluating phenytoin, clonazepam or clobazam appear to have been published; consequently, these medicines were not reviewed.

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Discussion

Whilst the hypothesis of GABAergic dysfunction in autism is strongly supported by research, of the thirteen reviewed studies comparing GABA modulator monotherapy with placebo, four studies reported no significant difference between the GABA modulator group and the placebo group (Berry-Kravis et al., 2012, 2017; Chez et al., 2002, Veenstra-VanderWeele et al., 2016). Only a few clinical trials appear to be investigating potential GABA modulators and they have so far yielded varied and ambiguous results (Brondino et al., 2016). GABA modulators that were evaluated by means of open-label trials produced serious biases i.e., absence of blinding and reporting bias, and endpoint measures in these trials depended on parent reports which could have likely caused expectancy biases (Brondino et al., 2016). However, it should be noted that GABA modulators are a very broad class of medications with diverse actions. Overall though there was a low risk of bias with the identified studies (Figures 1 and 2), which is encouraging.

Of the two studies investigating the efficacy and tolerability of the combination use of GABA modulators and antipsychotic medication, one study involving children using topiramate and risperidone demonstrated a significant improvement on ABC-Irritability (Rezai et al., 2010). The other study demonstrated a significant improvement in the ABC-Community subscale score for hyperactivity/non-compliance in children pretreated with L-carnosine versus children pretreated with placebo (Hajizadeh-Zaker et al., 2017). The study of Rezai et al. suggests a possible prophylactic efficacy of topiramate on irritability associated with risperidone in patients with ASD. L-carnosine combined with risperidone may also have a synergetic effect on ameliorating hyperactivity. However, due to heterogeneity of these studies, more research is needed before any recommendations can be made regarding clinical practice. Trials with valproate appeared favourably designed and produced promising results (Hollander et al., 2006, 2010), which also need to be investigated further.

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Arbaclofen and bumetanide were the medicines most studied. Disappointedly though, RCTs on arbaclofen failed to yield the desired results (Berry-Kravis et al., 2012, 2017; Veenstra-VanderWeeele et al., 2016). The largest study on arbaclofen (Veenstra-VanderWeele et al., 2016) did not obtain a significant difference in the primary endpoint measure (ABC-Social Withdrawal score), which resulted in a major disappointment in autism research. Fortunately, the $GABA_B$ agonist significantly improved other endpoint measures including the ABC-Social Avoidance subscale in patients with FXS (Berry-Kravis et al., 2012).

The only double blind RCT on bumetanide (Lemonnier et al. 2012) investigated the change in ASD symptoms using more accurate and specific measures (CARS and Autism Diagnosis Observation Schedule (ADOS)). The diuretic significantly reduced both the CARS and ADOS values, and thus making it a promising therapeutic drug to treat ASD. The other trials on bumetanide were open-label and with very small sample sizes (Hadjikhani et al., 2013; Lemonnier and Ben-Ari, 2010). In these trials, improvements in emotional processing and behavioural symptoms of infantile autistic syndrome supported bumetanide in being a promising treatment for social interactions in ASD.

However, the sample sizes in all the trials were, as a whole, small (some due to dropouts) causing problems with interpretation despite the low risk of bias. In addition, most of the documented trials allowed concomitant psychotropic drugs which could have affected the possibility to detect a real effect of the studied drug. Trials on some of the studied drugs were infrequent. The carnosine trial (Chez et al., 2002) was well designed but limited by small sample size, which may have contributed to the lack of efficacy observed in patients with ASD.

Other potential reasons for the lack of efficacy of the GABA modulators could be due to the appreciable heterogeneity of autism, symptoms vary distinguishably in quality and severity among patients, and it may be hard to measure significant change with a single endpoint. It is also likely that studies could have been affected by the inclusion of patients with a wide intelligence quotient range or

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with high level of aggressiveness or irritability. Consequently, meta-analysis could not be conducted in this review. In future studies, we believe it is important to have clearer characterisation of study participants with more restrictive inclusion criteria.

In addition, GABA dysfunctions may not be present in each ASD patient (Li et al., 2012). It is argued that a potential predictor of the efficacy of GABA modulators is the existence of a primitive GABA impairment. Consequently, electroencephalography (EEG) characterisation of participants could be a potential marker of treatment outcome and success with the reviewed medicines. In contrary to this view, Hirota et al. have argued that screening of patients with ASD by EEG should not be recommended at present if there is an absence of seizure-like episodes or suggestive behaviours. In addition, the limited data in this systematic review suggest inadequate evidence to support the use of GABA modulators to treat autistic patients with abnormal/epileptiform EEGs. Only two studies identified by our review investigated EEG abnormalities in the study population (Hollander et al., 2010; Wang et al., 2017). Hollander and colleagues retrieved a sleep-deprived EEG at baseline for 17/27 children in their trial, though their sample size was too small to make valid conclusions. Wang and colleagues confirmed subclinical epileptiform discharges (SEDs) in each patient after EEG examination. At the 6-month follow-up, SEDs were absent in 24/32 patients in the treatment group and 5/35 patients in the control group. Both studies suggest that autistic patients with abnormal/epileptiform EEGs would respond more effectively to antiepileptic drugs than autistic patients with normal EEG records. However, this needs further confirmation.

None of the reviewed studies used outcomes that assessed specifically compound-induced GABAergic effects. To date, most of the questionnaires are not relevant to psycho-pathological characteristics of ASD. Consequently, the design of more vigorous and specific outcome measures should be encouraged at as these measures may more effectively capture improvements in core symptoms to more effectively guide future treatment options.

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In conclusion, this systematic review supports that the fact that GABA modulators do provide a benefit for patients with ASD, mainly in hyperactivity, communication, and irritability. However, least in social withdrawal, social avoidance, and aggression. Further studies, particularly well-designed multicentre site studies with longer follow-up are necessary, especially in Africa, to clarify the efficacy of GABA modulators alone or in combination with other medications in order to guide future clinical practice. In the meantime, people affected with ASD in Africa should seek help from any regional autism organization for guidance and support if they exist. In addition, identification and possible care of these patients should be included within physician training and postgraduate studies in Africa.

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Conflict of Interest

No conflicts of interest, financial or otherwise, are declared by the authors.

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Table 1 Completed studies of GABA modulators in ASD

Study ID	n	Study design	Sample character	Diagnostic criteria	% male	N of patients in each arm	Follow-up period	Drug tested and dose	Other medication	Main findings	Outcomes	Adverse effects
Berry-Kravis et al., 2012	63	Randomised, double-blind, placebo-controlled, randomised	Outpatients aged 6-40 years with comorbid FXS	SB-5, ADI-R, DSM-IV	87.3	ACT: 30 PLA: 33	2 and 4 weeks	Arbaclofen maximum 20 mg/d (ages ≤12 years) and 30 mg/d (ages ≥13 years)	Up to 3 concomitant psychoactive medications (including antiepileptic drugs) were permitted	Improvements in social avoidance. No changes in irritability and aggression	ABC-I (secondary outcomes: ABC-LSW, ABC-SA, CGI-I, CGI-S, VAS, VABS-II)	Irritability
Berry-Kravis et al., 2012	27	Randomised, double-blind, placebo-controlled, randomised	Outpatients aged 6-40 years with more severe social impairment (ABC-LSW ≥8)	SB-5, ADI-R, DSM-IV	88.9	ACT: 27 PLA: 27	2 and 4 weeks	Arbaclofen maximum 20 mg/d (ages ≤12 years) and 30 mg/d (ages ≥13 years)	Up to 3 concomitant psychoactive medications (including antiepileptic drugs) were permitted	Improvements in social avoidance. No changes in irritability and aggression	ABC-LSW, ABC-SA, CGI-I, CGI-S, VABS-II	Irritability
Berry-Kravis et al., 2017	278	Randomised, double-blind, placebo-controlled	Outpatients with comorbid FXS aged 12-50 years (adolescent/adult study) and 5-11 years (child study)	DSM-IV	81.8	ACT: 189 PLA: 108	2-8 weeks	Arbaclofen maximum 30 mg/d (age range 5-11 years) and 45 mg/d (age range 12-50 years)	Up to 3 concomitant medications (except vigabatrin, tiagabine and riluzole and racemic baclofen) were permitted	No difference compared to placebo in both studies	ABC-C_{FX} (secondary outcomes: CGI-I, CGI-S, VAS, VABS-II, PSI, CSHQ)	Headache, nausea, vomiting, anorexia, irritability, anxiety, agitation, upper respiratory tract infection

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Table 1 continued

Study ID	n	Study design	Sample character	Diagnostic criteria	% male	N of patients in each arm	Follow-up period	Drug tested and dose	Other medication	Main findings	Outcomes	Adverse effects
Chez et al., 2002	31	Double-blind, randomized	Outpatients (age range 3-12 years) with prior diagnoses of ASD. Absence of known genetic comorbidity; no family history of seizures	DSM-IV-R	67.7	ACT: 17 PLA: 14	8 weeks	Carnosine 800 mg/d	NR	No difference compared to placebo	CGI, EOWPVT, ROWPVT, CARS, GARS	No serious adverse event
Erickson et al., 2013a	12	Pre-post study	Outpatients (age range 5-17 years; body weight ≥15 kg) with comorbid FXS	CGI-S, ADOS	83.3	–	2-10 weeks	Acamprosate initial dosage of 333 mg/day, increasing to a maximum of 1998 mg/d (if weight >50 kg) or 1332 mg/d (if weight <50 kg)	Non-glutamatergic psychotropic medications were allowed	Improvements in social skills and inattention/hyperactivity were observed	CGI-I (secondary outcomes: ABC-C, SRS, CY-BOCS-PDD, ADHD-RS-IV)	Irritability, increased repetitive behaviour
Erickson et al., 2013b	32	Open-label	Outpatients (age range 6-17 years) with prior diagnoses of either ASD or PDD and a score of ≥17 on the ABC-I subscale. Absence of genetic comorbidity associated with ASD. No family history of seizures	DSM-IV, ADI-R	90.6	–	8 weeks	Arbaclofen 20mg/d (ages ≤11 years) or 30 mg/d (ages ≥12 years)	Up to 2 concurrent psychotropic medications were allowed if dosing had been stable for at least 4 weeks	Improvements in irritability, social function, communication, social avoidance and motivation were observed	ABC-LSW, SRS, CYBOCS-PDD, CGI	Agitation, irritability, fatigue, psychomotor hyperactivity, insomnia, diarrhoea

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Table 1 continued

Study ID	n	Study design	Sample character	Diagnostic criteria	% male	N of patients in each arm	Follow-up period	Drug tested and dose	Other medication	Main findings	Outcomes	Adverse effects
Hadjikhani et al., 2015	7	Open-label	High-functioning patients with autism (n=2) and Asperger syndrome (n=5). Ages 19.3 ± 4.6 (mean ± SD) years	DSM-IV-TR, ADOS, ADI-R	100.0	–	10 weeks	Bumetanide 1 mg/d	NR	Improvement in emotional recognition and enhanced activation of brain regions involved in social and emotional perception during perception of emotional faces	fMRI, neuropsychological testing	Hypokalemia
Hajizadeh-Zaker et al., 2017	42	Double-blind, placebo-controlled	Outpatients aged 4-12 years with ASD	DSM-V, ABC-I, ADI-R	83.3	ACT: 21 PLA: 21	10 weeks	Carnosine 800mg/d	Risperidone maximum 1mg/d (if weight <20kg) or 2mg/d (if weight ≥20kg). Other treatments stopped at least 6 months before entering the trial	Reduction in hyperactivity was observed in the treated group. No improvements in irritability, lethargy/social withdrawal, stereotypic behaviour and inappropriate speech	ABC-C (primary outcome: ABC-I)	No serious adverse event
Hollander et al., 2006	13	Double-blind, placebo-controlled	Patients with autism (n=10), Asperger syndrome (n=2), and PDD (n=1). Average age 9.5 years (age range 5-40 years)	DSM-IV, ADOS, ADI-R	NR	ACT: 9 PLA: 4	1-8 weeks	Valproate (range 125-375 mg/d)	Psychoactive medication allowed if dose remained stable for at least 3 months prior to and during the trial	Reduction in time spent engaged in repetitive behaviours	CY-BOCS	Irritability, weight gain, anxiety, aggression

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Table 1 continued

Study ID	n	Study design	Sample character	Diagnostic criteria	% male	N of patients in each arm	Follow-up period	Drug tested and dose	Other medication	Main findings	Outcomes	Adverse effects
Hollander et al., 2010	27	Randomized, double-blind, placebo-controlled	Outpatients aged 5-17 years with ASD	DSM-IV-TR, ADOS-G, ADI-R	NR	ACT: 16 PLA: 11	2-12 weeks	Valproate maximum of 500 mg/d (if weight <40 kg) to 1000 mg/d (if weight ≥40 kg)	NR	Effective in treating irritability in ASD. No change in CGI-I autism	ABC-I, CGI-I (secondary outcomes: CY-BOCS, MOAS)	Nausea, vomiting, stomaches, appetite changes, dizziness, tremors, confusion, headaches, hair loss, weight gain
Lemonnier and Ben-Ari, 2010	5	Open-label	Outpatients (age range 3 years and 8 months to 11 years and 5 months) with infantile autistic syndrome	ICD-10, ADI-R	80.0	–	3 months	Bumetanide 1 mg/d	None	Improvements in autistic behaviour and communication in the participants after 3 months of treatment	CARS, ABC, CGI, RDEG, RRB	None
Lemonnier et al., 2012	54	Double-blind, randomized, placebo-controlled	Outpatients aged 3-11 years with autism or Asperger syndrome	ADI-R, ADOS-G	81.5	ACT: 60 PLA:60	3 months	Bumetanide 1 mg/d	Other treatments (except melatonin 1-4 mg) stopped at least 3 weeks before entering the trial	Amelioration of severe autistic symptoms and enhanced communication	CARS (secondary outcomes: CGI, ADOS-G)	Mild hypokalemia

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Table 1 continued

Study ID	n	Study design	Sample character	Diagnostic criteria	% male	N of patients in each arm	Follow-up period	Drug tested and dose	Other medication	Main findings	Outcomes	Adverse effects
Lemonnier et al., 2017	88	Double-blind, placebo-controlled	Patients with ASD spanning across the entire paediatric population (age range 2-18 years) were subdivided in four age groups. Participants with epilepsies were excluded	ICD-10, ADI-R, ADOS-G	88.6	ACT: 65 PLA: 23	4 months	Bumetanide 0.04-0.16 mg/kg/d (<25 kg) or 1-4 mg/d (≥25 kg)	Psychotropic medications were discontinued at least 4 weeks before entering the trial. Other medication except melatonin were prohibited	Improvement in ASD-related symptoms in across the paediatric age range	CARS (secondary outcomes: CGI, SRS)	Diuresis, anorexia, dehydration, fatigue, hypokalemia
Rezaei et al., 2010	40	Double-blind, randomized, placebo-controlled	Outpatients aged 3-12 years with ASD	DSM-IV-TR, ABC-C, ADI-R	67.5	ACT: 20 PLA: 20	8 weeks	Topiramate maximum 100mg/d (if weight <30kg or ages 3-6) or 200mg/d (if weight >30kg or ages 7-12)	Risperidone maximum 2mg/d (if weight 10-40kg) or 3mg/d (if weight >40kg)	Reductions in irritability, stereotypic behaviour and hyperactivity were observed in the treated group. No improvements in lethargy/social withdrawal and inappropriate speech	ABC-C	Somnolence, decreased appetite

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Table 1 continued

Study ID	n	Study design	Sample character	Diagnostic criteria	% male	N of patients in each arm	Follow-up period	Drug tested and dose	Other medication	Main findings	Outcomes	Adverse effects
Veenstra-VanderWeele et al., 2016	150	Double-blind, randomized, placebo-controlled	Outpatients aged 5-21 years with autistic disorder (n=130), Asperger syndrome (n=17) and PDD-NOS (n=3). Absence of seizures for at least 6 months before the trial. Absence of a known genetic disorder of ASD (FXS); no sensitivity to racemic baclofen	DSM-IV-TR, ADOS, SB-5	82.7	ACT: 76 PLA: 74	2, 4, 8 and 12 weeks	Arbaclofen maximum 45 mg (ages >12 years) or 30 mg (ages <12 years)	GABA agonists (except benzodiazepines), vigabatrin, tiagabine, riluzole, propranolol, anxiolytics/antidepressants, antipsychotics, or treatment with more than 2 psychoactive medications were prohibited	No significant difference was observed between arbaclofen and placebo on the primary outcome, ABC-LSW. Positive change in global ASD symptoms was seen in the treated children	ABC-LSW (secondary outcomes: CGI-I, CGI-S, ABC-C, VAS, VABS-II, ADHD-RS-IV)	Well tolerated
Wang et al., 2017	67	Double-blind, randomized	Paediatric inpatients aged 4-6 years with ASD and were diagnosed with SEDs; absence of seizures, other neurodevelopmental disorders and cerebral parsley	DSM-V	85.1	ACT: 32 PLA: 35	6 months	Levetiracetam 60 mg/kg/d	No other medication was permitted during the trial period	Improvements in cognitive, behaviour and language skills	PEP-3, CARS, ABC	Fatigue, somnolence, irritability

ABC-C: Aberrant Behaviour Checklist-Community Edition; **ABC-C_{FX}**: Aberrant Behaviour Checklist-Community Edition, FXS-specific; **ABC-I:** Aberrant Behaviour Checklist-Irritability; **ABC-LSW:** Aberrant Behaviour Checklist-Lethargy/Social Withdrawal; **ABC-SA**: Aberrant Behaviour Checklist-Social Avoidance; **ACT:** active drug; **ADHD-RS:** Attention Deficit Hyperactivity Disorder-Rating Scale; **ADI-R:** Autistic Diagnostic Interview-Revised; **ADOS:** Autism Diagnosis Observation Schedule; **ADOS-G:** Autism Diagnosis Observation Schedule-Generic; **ASD**: Autistic Spectrum Disorder; **CARS:** Childhood Autism Rating Scale; **CGI-I**: Clinical Global Impression of Improvement**; CGI-S**: Clinical Global Impression of Severity; **CSHQ:** Children's Sleep Habits Questionnaire; **CY-BOCS:** Children's Yale-Brown Obsessive Compulsive

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Scale; **DSM-IV:** Diagnostic and Statistical Manual of Mental Disorders**,** 4th Edition; **DSM-IV-R:** Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Revised; **DSM-IV-TR:** Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision; **DSM-V:** Diagnostic and Statistical Manual of Mental Disorders**,** 5th Edition; **EOWPVT:** Expressive One-Word Picture Vocabulary Test; **fMRI**: functional magnetic resonance imaging; **FXS**: fragile X syndrome **GARS:** Gilliam Autism Rating Scale; **ICD-10:** International Statistical Classification of Diseases and Related Health Problems, 10th Revision; **MOAS:** Modified Overt Aggression Scale; **NR:** not reported; **PDD:** pervasive developmental disorder; **PEP-3:** Psychoeducational Profile, 3rd Edition; **PSI**: Parenting Stress Index; **RDEG:** Regulation Disorder Evaluation Grid; **ROWPVT**: Receptive One-Word Picture Vocabulary Test; **RRB:** Repetitive and Restricted Disorder; **SB-5:** Stanford-Binet Intelligence Scales, 5th Edition; **SED:** Subclinical epileptiform discharge; **SRS:** Social Responsiveness Scale; **VABS-II:** Vineland Adaptive Behaviour Scale, 2nd Edition; **VAS:** Visual Analogue Scale

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Table 2 Ongoing trials

Study ID	n	Study design	Sample character	Diagnostic criteria	% male	N of patients in each arm	Follow-up period	Drug tested and dose	Other medication	Main findings	Outcomes	Current status
NCT01813318	36	Randomized, double-blind, placebo-controlled	Outpatients aged 5-23 years with diagnostic confirmation of ASD	ABC-SW, CGI-S	–	–	10 weeks	Acamprosate maximum 1998 mg/d (if weight >50kg) and 1332 mg/d (if weight <50kg)	Up to 2 concomitant psychotropic drugs (stable dosing for >60 days) not impacting glutamate or GABA-A neurotransmission is allowed	–	ABC, CGI-I	Recruiting
NCT01911455	48	Randomized, double-blind placebo-controlled	Outpatients aged 5-23 years) with diagnostic confirmation of full mutation FXS. Absence of seizures. Normal kidney function	NR	–	–	10 weeks	Acamprosate maximum 1998 mg/d (if weight >50kg) and 1332 mg/d (if weight <50kg)	Up to 2 psychotropic medications are permitted (unstable dosing is not allowed). No change in anti-epileptic drug dosing for 60 days prior to study	–	ABC-SW (secondary outcomes: CGI-I, ABC-H, ABC-SA)	Recruiting
NCT02278328	40	Randomized, double-blind placebo-controlled	Right-handed males aged 14-17 years diagnosed of ASD within the last 12 months, including autism, PDD-NOS, and Asperger syndrome but excluding childhood dis-integrative disorder and Rett syndrome	DSM-IV	100%	–	4 weeks	STX209 (arbaclofen) maximum 30 mg/d	Current pharmacological treatment regimen has been stable for at least 4 weeks prior to screening. Racemic baclofen, vigabatrin, tiagabine, or riluzole are prohibited	–	Magnetoence phalography	Recruiting

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Table 2 continued

Study ID	n	Study design	Sample character	Diagnostic criteria	% male	N of patients in each arm	Follow-up period	Drug tested and dose	Other medication	Main findings	Outcomes	Current status
NCT00211796	10	Open label	Outpatients, both male and female (age range 18-65 years) must meet DSM-IV, ADI, or ADOS criteria for ASD. Absence of seizures	DSM-IV, ADI, ADOS	–	–	12 weeks	Valproate (extended release)	Psychotropic medication allowed if dose remained stable for at least 3 months prior to and during the trial	–	CGI-I, CGI-S, MOAS, ALS (secondary outcomes: GAF, AQ, Ham-D, YBOCS, ABC, BIS-11)	Unknown

ABC-H: Aberrant Behaviour Checklist-Hyperactivity; **ADI:** Autism Diagnostic Interview; **ADOS:** Autism Diagnostic Observation Schedule; **ALS:** Affective Liability Scale; **AQ:** Aggression Questionnaire; **BIS-11:** Barratt Impulsiveness Scale Version 11; **GAF**: Global Assessment of Functioning Scale; **Ham-D:** Hamilton Depression Scale; **MOAS:** Modified Overt Aggression Scale; **PDD-NOS:** Pervasive Developmental Disorders-Not Otherwise Specified; **YBOCS:** Yale Brown Obsessive Compulsion Scale

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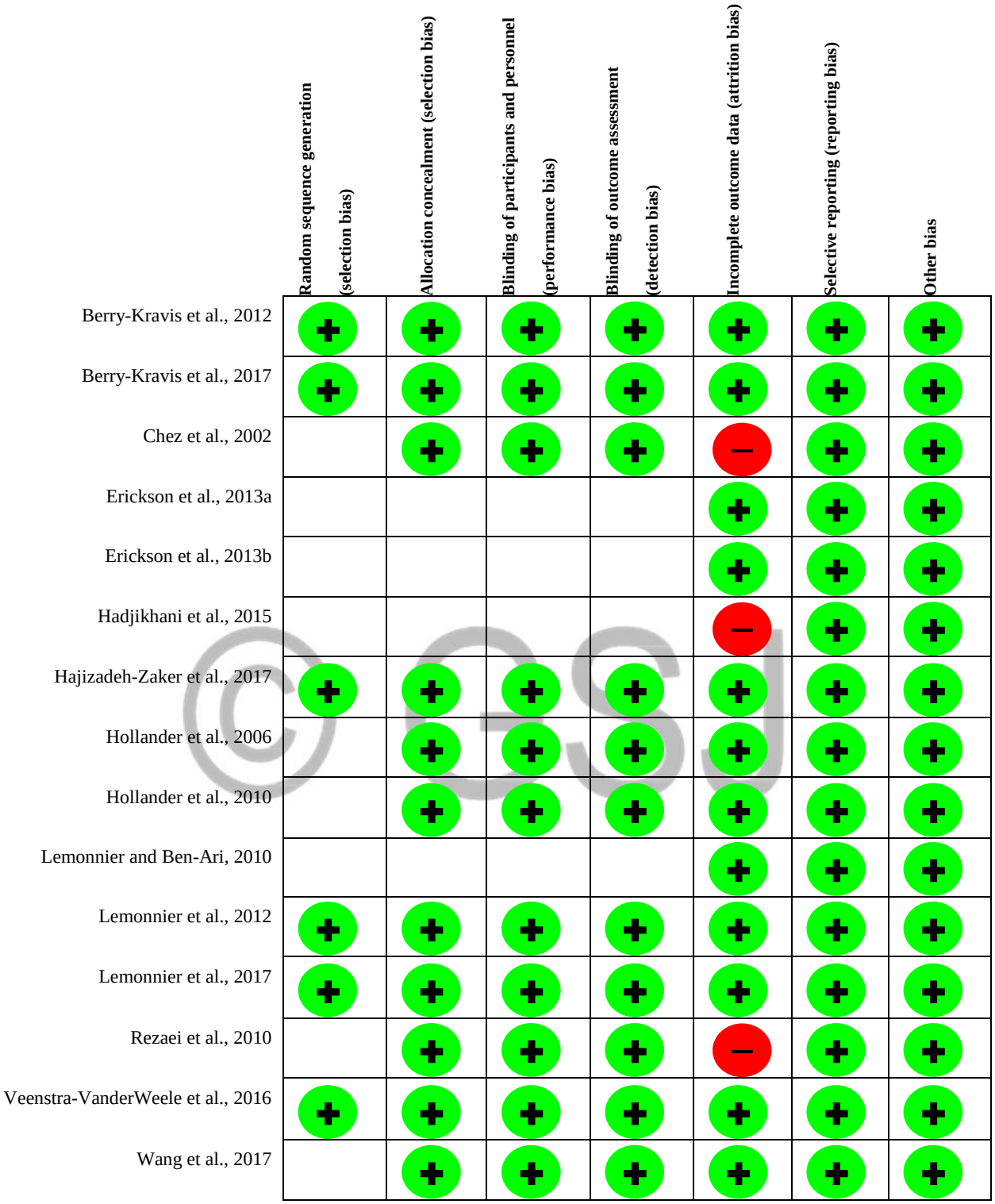

Figure 1 Risk of bias summary of included studies (*green circle* low risk of bias, *red circle* high risk of bias, *blank* unclear risk of bias)

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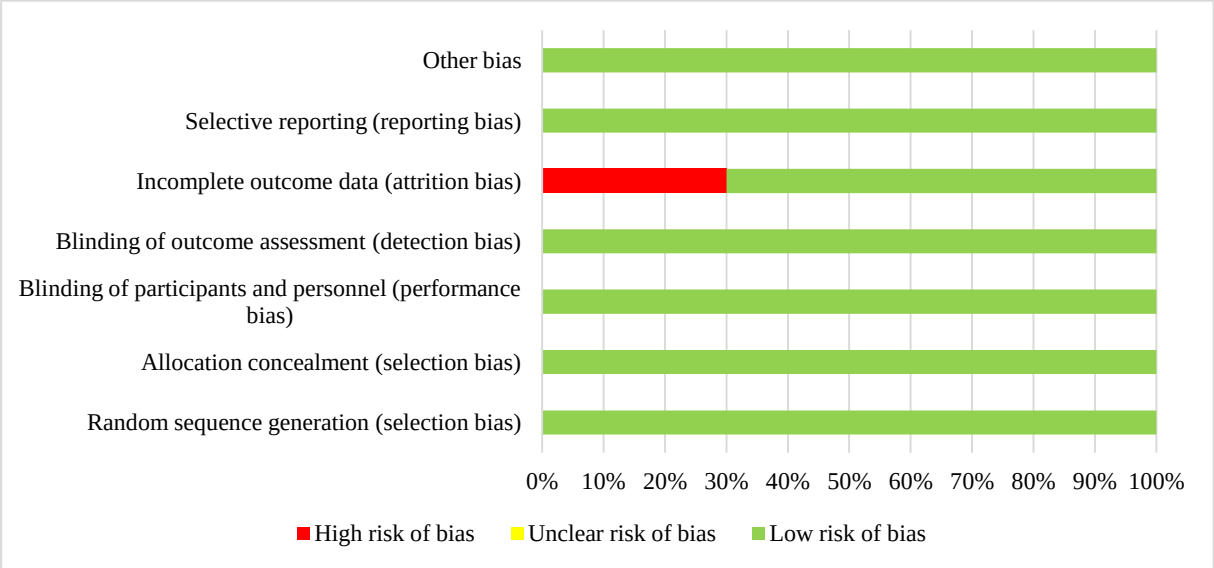

Figure 2 Risk of bias graph of the included studies

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