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Review

Pharmacological treatment for challenging behavior in adults with intellectual disability: Systematic review and meta-analysis

Rodrigo Campos-Jara [a], Cristian Martínez-Salazar [b], Christian Campos-Jara [c], José María Fernández [a], Darío Martínez-García [d], Falonn Contreras-Osorio [c,*]

[a] Psychiatry Department, Hospital Mauricio Heyermann, Angol 4650207, Chile
[b] Department of Physical Education, Sports, and Recreation, Pedagogy in Physical Education, School of Education and Social Sciences and Humanities, Universidad de La Frontera, Temuco 4780000, Chile
[c] Exercise and Rehabilitation Sciences Institute, Faculty of Rehabilitation Sciences, Universidad Andres Bello, Santiago 7591538, Chile
[d] Department of Physical Education and Sports, Faculty of Sport Sciences, University of Granada, 18011 Granada, Spain

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ABSTRACT

Introduction: Few evidence on the use of antipsychotics in people with intellectual disabilities and challenging behaviors, generates the need to develop studies that contribute to collect, compare and synthesize the available information. The present systematic review and meta-analysis aims to determine the clinical efficacy of antipsychotic medication in reducing critical episodes in this population.
Methods: We searched Web of Science, Scopus, EBSCO, Embase, and PubMed for randomized controlled trials of antipsychotic medication versus placebo. Preliminarily yielded 1354 abstracts and citations; six studies with 274 subjects met the inclusion criteria of studies with experimental design, longitudinal type, with pre- and post-intervention measurements.
Results: There is evidence for the use of psychotropic drugs in the acute management of challenging behaviors in patients with intellectual disability (SMD = −0.85; 95% CI = −1.69 to −0.01; $p = 0.05$).
Conclusions: Our results coincide with the recommendations on the efficacy of the use of antipsychotics. Although our study provides evidence, the limited number of studies included in this research does not allow us to obtain totally conclusive results, although it can be considered as a guide for future studies.

Introduction

People with intellectual disability present deficits in neurological development associated with limitations in their intellectual functioning and adaptive behavior.[1] These manifestations appear before 18 years of age, as the main taxonomies DSM V[2] and CIE 10[3] describe.

Roughly between 10 and 20% of adults with intellectual disability who live in the community present challenging behaviors, including aggression, socially inappropriate behaviors, self-harm, destructive behavior or stereotyped behaviors.[4–6] These behaviors in patients with intellectual disability may reflect a limited ability to respond to adversity, demonstrating less resilience and more deficient coping strategies than the rest of the population.[7]

The prescription of psychotropic drugs for people with intellectual disability often includes excessive dosage and duration of treatment, being used to control the challenging behavior,[8–11] even without a history of serious mental disease or comorbidity with a psychiatric diagnosis.[11–13] The possible explanations for this finding could be an increase in challenging behaviors and/or the unnecessary prolongation of this prescription.[14,15]

The construction of intervention strategies in people with intellectual disability and challenging behaviors should consider prevention mechanisms and the social context, without focusing solely on the demonstrated challenging behaviors, to favor the creation of long-term comprehensive treatments.[7,16–18]

Previous systematic reviews have analyzed variables such as efficacy, effectiveness, adverse effects, and the evidence related to both the reduction and discontinuation of antipsychotic medication in people with intellectual disability and challenging behaviors.[14,18–22] However, to date the evidence contributed by research is inconclusive with respect to the specific benefits for this population, and there is insufficient evidence to recommend phar-

* Corresponding author.
E-mail address: falonn.contreras@unab.cl (F. Contreras-Osorio).

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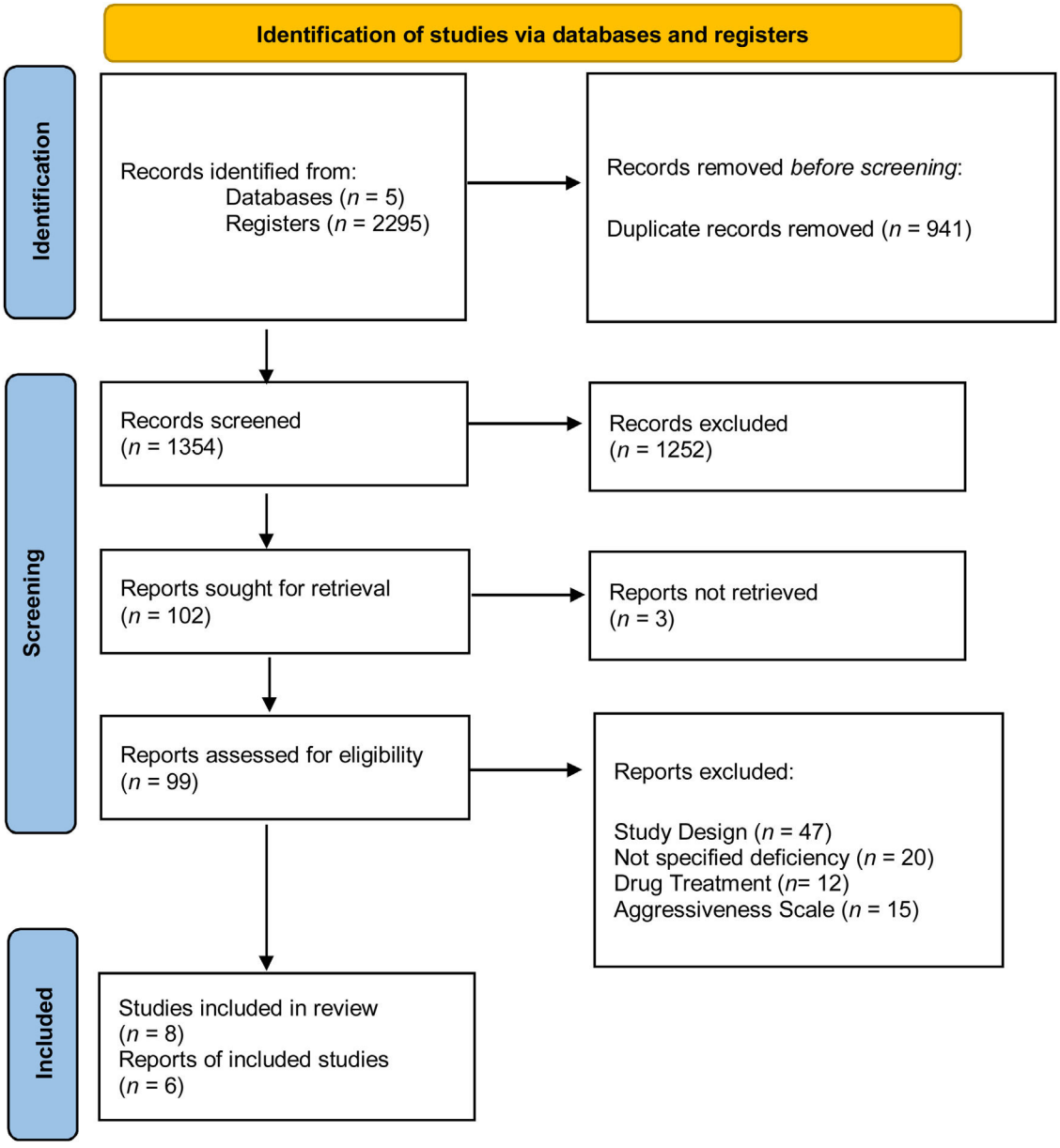

Figure 1. Flow diagram of the studies included in the meta-analysis.

macological treatments that reduce concrete behavioral issues. In this light, the need to develop studies that contribute to collecting, comparing and synthesizing the available data on this subject persists, safeguarding methodological aspects that make it possible to draw reliable conclusions.

Therefore, this systematic review and meta-analysis seeks to determine the clinical efficacy of antipsychotic medication in reducing critical episodes in people with intellectual disability and challenging behaviors.

Materials and methods

A systematic review was carried out on 1 June 2021 to search the published scientific evidence to understand how medication can improve aggressive behavior in individuals with intellectual disabilities. Before starting the review, a protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) registration number CRD42022322066. The reporting flow diagram of this systematic review was based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines[23] (Fig. 1).

Search strategy

Randomized control trials (RCT) were identified by searching the five principal electronic databases: Web of Science, Scopus, EBSCO, Embase, and PubMed. The bibliographic search was carried out by combining the different medical subject heading (MeSH) terms with the following keywords: Aggressions, "Agonistic Behavior", Hostility, "Challenging behavior", "Assaultive Behavior", "Drug Therapy", "Psychotropic Drugs", "Tranquilizing Agents", Psychopharmaceutical, "Psychotropic medication", "Intellectual Disability", "Mental Retardation", "Mental Deficien*". These search terms were combined with two Boolean operators: AND and OR. Additionally, the bibliographies of other previous related reviews and the studies ultimately selected were examined to search for new studies. Other possible scientific evidence related to

the subject was identified by contacting authors of the published articles via email.

Two independent reviewers (RC and JMFU) examined the title and abstract of the articles found in the databases. After the initial selection, they analyzed each study with the inclusion criteria. Each criterion was evaluated as yes or no. If discrepancies existed between the authors, the ratings of the articles were shared and discussed until a consensus was reached with a third reviewer (DMG). The authors were familiar with the existing literature and were not biased toward any of the studies selected for inclusion in the review.

Inclusion criteria

The eligibility of each investigation was measured according to the following inclusion criteria: (a) adult subjects with intellectual disabilities; (b) medication treatment for challenging behavior; (c) randomized control trial as a study design; (d) behavior outcomes measured with at least one scale; (e) the study had to have sufficient data to calculate effect sizes (ES). The articles that met the inclusion criteria were identified, and their full-text versions were obtained.

Data extraction process

Two independent authors (RC and JMFU) extracted the data according to a previously established protocol. A third reviewer (DMG) discussed the study data if differences or inconsistencies were found until an agreement about the data validity was made. The following information was collected: (1) author's name and year of publication; (2) sample size and gender of participants; (3) intellectual disabilities; (4) subjects' age; (5) medication treatment and follow up of any side effects; (6) challenging behavior measurements; (7) the limitations, suggestions, applications, and conclusions described in the studies.

Risk of bias in individual studies

The risk of bias (RoB) assessment was performed using the Cochrane RoB tool.[24] This tool assesses the RoB according to seven domains: generation of the random sequence, concealment of the randomization sequence, blinding of participants and treatments, blinding of the evaluation of the results, incomplete results, selective reporting of results, and other sources of bias. Each domain is rated as "low," "unclear" or "high" RoB. The methodological quality of the studies included was independently reviewed by two reviewers—DMG and FCO—and any discrepancies between them were resolved by consensus with a third reviewer (RCJ).

The synthesis and quality of evidence for each outcome were performed with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).[25] The quality of the evidence was classified into four categories: high, moderate, low, and very low. We used the GRADE profiler (GRADEpro) to import the data from RevMan 5.4 to create a "summary of findings" table.

All studies meeting the inclusion criteria were incorporated into the review, regardless of their methodological quality or risk of bias.

Strategy for data synthesis

All calculations were conducted using a Microsoft Excel (Microsoft, Redmond, WA, USA) spreadsheet containing data extracted from each publication. Review Manager (RevMan) version 5.3.5 was used for all the statistical analyses' forest plot. The Cochran Q statistic[26] was used to assess heterogeneity between studies. Heterogeneity is a measure of the differences in main effects between studies. Additionally, I^2 statistics were used to evaluate heterogeneity ($I^2 > 50\%$).

Medication treatment on individuals with intellectual disabilities and their effect over challenging behavior outcomes were calculated for each included study, following coding of the between-group post differences and standard deviations (SD). The standardized mean difference (SMD), which is the difference between the experimental and control groups divided by the pooled standard deviation, was calculated to see the effect size. Random-effects inverse variance (IV) was used with the measurement of the effect of SMD.

The analysis of ES was conducted with a random-effects model estimated using the DerSimonian and Laird method.[27] A random-effects model is incorporated when the assumption is that the data demonstrated effects, across studies, that are randomly situated around a central value. Forest plot was generated to demonstrate the specific effects of between-group differences on challenging behavior differences and ESs within the respective 95% CI. Combining estimates then allowed for the assessment of a pooled effect. The reciprocal sums of two variances were accounted for, including the estimated variance associated with the study and the estimated variance component due to the variation between studies. A sensitivity analysis was conducted to identify highly influential studies that might have biased the analysis.

The study-specific weight was derived as the inverse of the square of the respective standard errors. ESs of ≤ 0.2, ≤ 0.5, ≤ 0.8, and ≥ 0.8 were considered trivial, small, moderate, and large, respectively.[28]

Results

The flow diagram of the article searches and selection is depicted in Fig. 1, from the systematic search to inclusion.

Study selection

The preliminary search yielded 1354 relevant abstracts and citations. The full texts of 102 articles were deemed to meet the inclusion criteria. From these 99 studies were rejected for this meta-analysis for the reasons seen in Fig. 1. Finally, six studies met the inclusion criteria (Table 1). The experimental design of the included studies was a longitudinal study with pre- and post-intervention measurements.

Risk of bias in individual studies

The RoB assessment is presented in Fig. 2. The selection bias (lack of or inadequate random generation and allocation concealment of participants) was rated as low risk in five studies for at least one of the evaluated parameters.[29–33] The performance bias (lack of or inadequate blinding of participants and personnel) was rated as low risk in four of the six included studies.[29,32–34] The detection bias was low in all included studies. Bias due to incomplete outcome data was low in only one study.[34] The reporting bias was rated as low risk in three studies.[29,30,32] Finally, other biases were rated as unclear in all included studies.

Confidence in cumulative evidence

The overall quality and summary of evidence with the GRADE approach are shown in Table 2, with a high rating for the use of antipsychotic medication in reducing critical episodes in people with intellectual disability and challenging behavior.

Study characteristics

Participants' ages ranged from 18 years to 60 years. 5 of the 6 included studies incorporated both men and women in their

Table 1
Subjects' characteristics from the included studies.

Reference	*N*	Sex	Age (years)	Intellectual disability	Comorbidity
Amore et al., 2011[29]	N = 62; EG1 = 31, EG2 = 31	M = 45; F = 17	48 ± 12.45	Severe (DSM-IV TR)	Not reported
Elie et al., 1980[30]	N = 51; EG1 = 17, EG2 = 17, PG = 17	M = 33; F = 18	32.9 ± 2.5	IQ 33.2 ± 3.29	Epilepsy
Lynch et al., 1985[31]	N = 30; EG = 15, PG = 15	M = 21; F = 9	37.1 ± 12.1	Unspecified level (CGI)	Not reported
Ramerman et al., 2019[32]	N = 25; EG = 14, PG = 11	EG: 10M/4F; PG: 9M/2F	EG: 28 ± 16.1; PG: 33 ± 20.16	IQ < 70	None
Tyrer et al., 2008[33]	N = 86; EG1 = 29, EG2 = 28, PG = 29	M = 53; F = 33	26–55	IQ < 75	Autism
van Hemert, 1975[34]	N = 20; EG = 10, PG = 10	F = 20	22–42	Moderate = 9; Severe = 10; Profound = 1 (DSM II)	Not reported

N: number of subjects; M: male; F: female; EG: experimental group; PG: placebo group; IQ: intelligence quotient; DSM-IV TR: Diagnostic and Statistic Manual-IV Edition Text Revision; CGI: Clinical Global Impression scale; ID: intellectual disability; DSM II: Committee on Nomenclature and Statistics of the American Psychiatric Association.

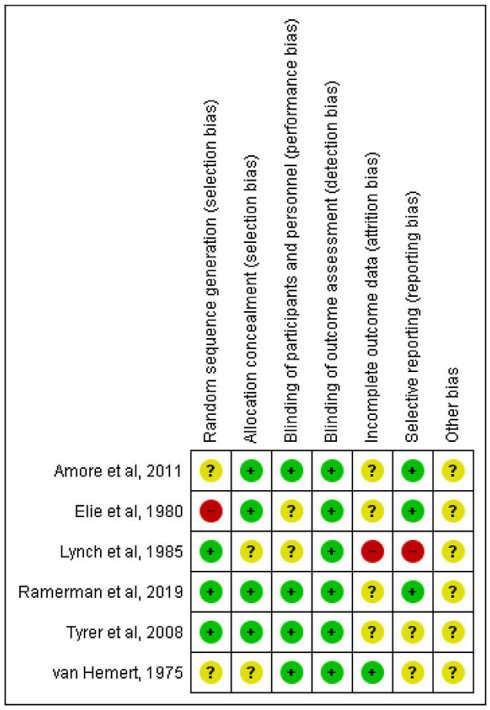

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study. Low risk of bias; high risk of bias; unclear risk of bias.

sample; however, one incorporated women exclusively. Due to overlapping samples in the study design, the samples of Ellie (1980) and Tyrer (2008) were divided by 2. In addition, the study of Amore (2011) conducted a two parallel-arm study where the control groups were each other's washout period respectively. Interventions consisted of medication administration, with risperidone being the most commonly used. Of the 6 studies, challenging behavior was measured with psychiatric tests in all of them, with Clinical Global Impression scale (CGI) and Target Symptom Aggressivity (TSA) being the most used. The total duration of the programs ranged up to 26 weeks of follow-up. One study was performed in an inpatient center while two others were conducted with patients in institutional settings. Two studies were conducted in outpatient centers, and one did not indicate the location (Table 3).

Effects of drugs on challenging behavior

Eight intervention groups were included to perform the meta-analysis of the effect of psychoactive drugs on aggressive behavior in patients with intellectual disability. The global estimation of the grouped SMD showed significant differences for psychoactive drug use for the treatment of aggressive behaviors in people with intellectual disability, obtaining a large effect size (ES) (SMD = −0.85; 95% CI = −1.69 to −0.01; $p = 0.05$) with a substantial heterogeneity ($I^2 = 93\%$, $p < 0.00001$) (Fig. 3).

Discussion

The management of challenging behavior in patients with intellectual disability is a challenge at present both in the community and in the hospital units where many of these users are admitted to manage this behavior after not responding to environmental management or psychosocial strategies. The results of our review show that there is sufficient evidence to recommend the use of psychotropics, mainly the so-called "antipsychotics" group or dopamine blockers in such acute actions in response to this problem (SMD = −0.85; 95% CI = −1.69 to −0.01; $p = 0.05$) because they are useful in the acute handling of challenging behaviors in patients with intellectual disability.

Various systematic reviews have previously sought to establish a recommendation, but most from a pediatric approach; there are fewer works available in the literature on adults. Even with differences in the populations analyzed, the main results of the reviews on the subject are that there may be an indication where these antipsychotics would be useful to deal with aggressive behaviors acutely, agreeing with previous research.[16,35,36]

In comparison with other reviews, for example, the work by Brylewski et al.,[35] which included data on patients under 18 years as well as adults, we made a distinction from behavioral structuring and intellectual condition without appealing to development. In the work by Matson et al.,[16] there is consensus on the paucity of cited works of greater rigor, in addition to suggesting a long-term follow-up to evaluate the benefits; however, that study was prepared as a narrative review and establishes recommendations from the opinion of the expert in the discussion. The distinction we make from the clinical and functional point of view of adults with intellectual disability considered a challenging behavior structure, which is different from Sawyer et al.,[36] since it is not characteristic clinically or functionally on the autism spectrum.

As an intervention, from a clinical point of view in the perspective of acute response and level of evidence, we concentrated on antipsychotics as the main tool. Sawyer et al.[36] analyzed the use of fluvoxamine, sertraline, clomipramine, risperidone and ziprasidone to reduce challenging behaviors, showing that risperidone was more effective in short- and long-term treatment. Thus, when administering constant reduced doses of antipsychotics after an acute episode, it becomes a distinguishable treatment from the placebo,[33] without establishing a standard dose in the acute context.

In the text by Brylewski et al.,[35] where assessing the change of behavior was evaluated as a secondary result, they were only able to extract data with respect to the unspecific general improvement in behavior. In this sense, our intention was to arrive at a single scale, which is difficult due to the polymorphous nature of the challenging behavior that can lead to variety of assessment scales, finding in

Table 2
Summary of findings and quality of evidence (GRADE) of clinical efficacy of antipsychotic medication in reducing critical episodes in people with intellectual disability and challenging behavior.

Certainty assessment							N° of patients		Effect		Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Challenging behavior	Placebo	Relative (95% CI)	Absolute (95% CI)		
6	Randomized trials	Serious	Not serious	Not serious	Serious	Strong association all plausible residual confounding would reduce the demonstrated effect	171	169	–	SMD 1.68 lower (3.12 lower to 0.24 lower)	High	Important

CI: confidence interval; SMD: standardized mean difference.

Table 3
Intervention characteristics of the included studies.

Studies	Setting	Drug	Drug dosage	Intervention length	Other treatments	Outcome measures	Aggressiveness scale
Amore et al., 2011[29]	Residencial care	Olanzapine/ risperidone	10 mg of olanzapine or 4 mg of risperidone.	24 weeks	No additional treatments were reported.	Aggressive behaviors (OAS), clinical outcome (improvement subscale of the CGI), clinical neuroleptic-induced Parkinsonism symptoms (Simpson Angus Scale), neuroleptic-induced akathisia and tardive dyskinesia (Abnormal Involuntary Movement Scale, and Tardive Dyskinesia Rating Scale), side effects (Dosage Record and Treatment Emergent Symptoms Scale), clinical laboratory tests, weight, and cardiac abnormalities (electrocardiogram).	OAS, CGI
Elie et al., 1980[30]	Inpatients	Trepipram/ thioridazine	Trepipram 100 mg/thioridazine 50 mg	4 weeks	Use of anticonvulsants was maintained. Mesoridazine (50 mg) was authorized in case of uncontrollable aggressivity.	Severity of the aggressive manifestations (TSA), symptomatic evolution (CAM), therapeutic value of the drugs (CGI), hematology, electrocardiogram, biochemical and urinalysis tests.	TSA, CAM, CGI.
Lynch et al., 1985[31]	Unmentioned	Palmitate pipotiazine	25 mg	13 weeks	In the event of extremely disruptive or aggressive behavior, oral thioridazine was available as an emergency drug. Oral orphenadrine was authorized to be used in the event of extra-pyramidal side-effects.	Symptoms of aggressiveness (CGI, TSA), side-effects (Extrapyramidal Side-Effects Scale), and laboratory tests.	CGI, TSA
Ramerman et al., 2019[32]	Ambulatory	Risperidone	Average dose: 1.97 mg	24 weeks	All participants were allowed to use any kind of co-medication or receive any kind of psychosocial interventions if already ongoing before the trial.	Behavioral outcomes: irritability subscale of the ABC (primary outcome measure), other subscales of the ABC; changes in challenging behavior using CGI-I. Health parameters: sedation (Epworth Sleepiness Scale adapted), autonomic symptoms (Scale for Outcomes in Parkinson's disease for Autonomic Symptoms), weight, BMI, waist circumference, blood pressure, pulse, laboratory testing, and extrapyramidal symptoms (Abnormal Involuntary Movement Scale, Barnes Akathisia Rating Scale, and Unified Parkinson's Disease Rating Scale).	ABC, CGI-I
Tyrer et al., 2008[33]	Ambulatory multi-center	Risperidone/ haloperidol	1–2 mg/2.5-5 mg	26 weeks	Lorazepam up to 2 mg daily was permitted as a rescue medication in emergencies.	Aggressive behavior (main outcome) with the MOAS and the ABC (community version), effect on carers (uplift and burden scale), quality of life (40-item quality of life questionnaire), adverse drug effects (udvalg for kliniske undersogelser scale), and severity of illness (CGI).	MOAS, ABC, CGI
van Hemert, 1975[34]	Institutionalized	Pipamperone	80–240 mg/day	4 months	No additional treatments were reported.	Fits of anger, verbal aggressiveness, actual aggressiveness, fussiness, fugues, destructive disposition, dysphoria, impulsiveness, sleep disorders, and manageability.	RSTMR

TSA: Target Symptom Aggressivity; CAM: Chief Aggressive Manifestations; CGI: Clinical Global Impression Scale; MOAS: Modified Overt Aggression Scale; ABC: Aberrant Behavior Checklist; CGI-I: Clinical Global Impression Scale-Improvement; RSTMR: Rating Scale for Troublesome Mental Retardates; OAS: Overt Aggression Scale.

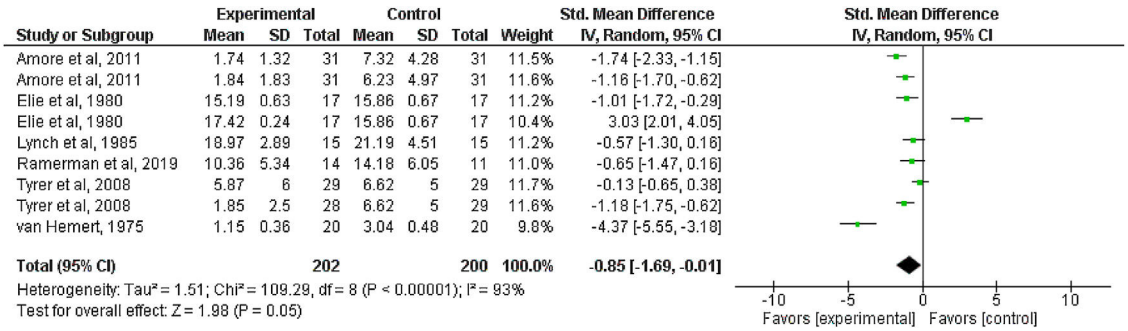

Figure 3. Forest plot of clinical efficacy of antipsychotic medication in reducing critical episodes in people with intellectual disability and challenging behaviors. The vertical line indicates the overall estimate of combined studies' standardized mean effect size. The horizontal line indicates 95% CI, squares indicate estimates, square size is proportional to sample size, and rhombus indicates meta-analytically pooled estimates' 95% CI. IV = inverse variance.

our investigation results on the following scales: Target Symptom Aggressivity (TSA), Chief Aggressive Manifestations (CAM), Clinical Global Impression scale (CGI), Clinical Global Impression Scale-Improvement (CGI-I), Overt Aggression Scale (OAS), Rating Scale for Troublesome Mental Retardates (RSTMR), Irritability subscale of the ABC (ABCis), and the Modified Overt Aggression Scale (MOAS). CGI and the TSA were used most frequently in the measurement of challenging behavior within the studies selected in the present review.

For a complete analysis of the contributions of this article, it is necessary to indicate the limitations present in it. The limited number of studies (clinical trials) and the small sample size of the included studies constrains the interpretation of the reported results, although it is possible to obtain some guidance on how to use drugs in critical clinical situations. Therefore, the above results may be used as a guideline for the design of future original studies on the matter. In addition, some studies are more than 10 years old, including tests with drugs that have been discontinued or are not currently in use (SCH-12679, thioridazine and pipamperone). In general, no follow-up has been conducted after the pharmacological treatment to ensure that the aggressive behavior did not vary after the experiment ended. In terms of design, only articles indexed in peer-reviewed journals, in Spanish or English and with an approach in adult psychiatry were taken into consideration; this situation may mean that some scientific evidence in other languages or present in the gray literature, such as doctoral theses or conference abstracts, was not incorporated.

Conclusion

Our work shows favorable evidence for the use of psychotropics for the acute handling of challenging behavior in patients with intellectual disability. In addition, some drugs showed greater evidence over others, among which risperidone is worth noting.

From the results obtained, for future studies, randomized controlled trials on the efficacy of the medication (antipsychotics) in the treatment of adults with intellectual disability and challenging behaviors are needed. These investigations must describe the procedure of randomization, blinding and the details of those who withdraw from the study early, while simultaneously noting the participants as to the demographic details of their populations of origin (prevalence, incidence) and the challenging behavior and secondary outcomes in clear language in the short and long term.

In this vein, the recommendation of an approach that combines the pharmacological and psychological makes it necessary to investigate the best tools and most effective psychological approaches to confront challenging behavior.

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