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ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

«Αξιολόγηση της αποτελεσματικότητας της μακράς δράσης Ρισπεριδόνης στη Σχιζοφρένεια: μία Consort-συμμορφωμένη αξιολόγηση Τυχαιοποιημένων Ελεγχόμενων δοκιμών».

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Λάρισα, 2025

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Assessing the Efficacy of Long-Acting Risperidone in Schizophrenia: A CONSORT-Compliant Evaluation of Randomized Control Trials (RCTs).

1 Abstract:

1.1 Background- Purpose

Schizophrenia is a chronic, often progressive, and severe mental disorder that typically requires continuous treatment with antipsychotic agents [5]. Risperidone was the first second-generation antipsychotic introduced in long-acting injection (RLAI). This study systematically evaluates randomized controlled trials (RCTs) on long-acting risperidone for schizophrenia, published between 2002 and 2025, using the CONSORT guidelines to assess reporting quality and methodological transparency. High- quality RCTs are essential, as they play a crucial role in evidence-based decision-making for clinical practice and policy development.

1.2 Methods

Using the PubMed database, we searched for RCTs involving patients with schizophrenia treated with long-acting risperidone, published between 2002 and 2025. The quality of reporting was assessed using a 37-item checklist based on the updated CONSORT 2010 guidelines. Compliance of ≥75% was considered optimal-adequate. The primary objective was to calculate the mean CONSORT compliance across the included RCTs and further analyze compliance using descriptive statistics. Secondary objectives included estimating compliance for each CONSORT item and analyzing potential determinants of reporting quality ―such as journal impact factor (IF), sample size, and the year of publication ― through univariate and multivariate analyses.

1.3 Results

Thirteen studies were eligible for evaluation. The mean CONSORT compliance was 77.34%± 12.89% (standard deviation). Among retrieved studies, nine (69.2%) achieved good reporting quality (≥75%), while four (30.8%), were presented with inadequate reporting (<75%). Among the 37 checklist items, 22 were reported by at least 75% of the studies. A statistically significant positive correlation was observed between publication year and CONSORT compliance (Spearman's $\rho = 0.772$, $p = 0.002$), indicating improved reporting quality over time. Univariate analysis failed to reveal statistically significant association between the reporting quality and the possible determinants: IF of journal [p=0.217, OR=10.5, 95%CI= (0.668-165.114)] or sample size [p= 0.266, OR=6, 95%CI= (0.422-85.248)]. Logistic regression failed to demonstrate significant predictors of reporting quality, though a higher impact factor and sample size showed a non-significant trend toward better adherence.

1.4 Discussion

The quality of RCTs on long-acting risperidone in schizophrenia appears to be adequate, with a generally good adherence to CONSORT guidelines. Furthermore,

our findings indicate an improvement in reporting quality over the years, suggesting that the incorporation of CONSORT recommendations has positively influenced RCT methodology.

Key-words: Randomized controlled trials, long-acting risperidone, TV-46000, RBP-7000, schizophrenia, CONSORT checklist

1. Περίληψη

1.1Εισαγωγή:

Η σχιζοφρένεια αποτελεί μια χρόνια, συχνά προοδευτική και σοβαρή ψυχιατρική διαταραχή που απαιτεί συνεχόμενη θεραπεία με αντιψυχωτική αγωγή [5]. Η ρισπεριδόνη είναι το πρώτο αντιψυχωτικό δεύτερης γενιάς που διατέθηκε σε μορφή μακράς δράσης (RLAI). Η παρούσα μελέτη αξιολογεί συστηματικά τυχαιοποιημένες ελεγχόμενες δοκιμές (RCTs) για τη μακράς δράσης ρισπεριδόνη στη σχιζοφρένια, οι οποίες δημοσιεύτηκαν μεταξύ 2002 και 2025, χρησιμοποιώντας τις κατευθυντήριες οδηγίες CONSORT 2010 για την εκτίμηση της ποιότητας αναφοράς και της μεθοδολογικής διαφάνειας. Οι υψηλής ποιότητας RCTs είναι ζωτικής σημασίας, καθώς διαδραματίζουν καθοριστικό ρόλο στην λήψη αποφάσεων στην κλινική πρακτική βάσει αποδείξεων και στην ανάπτυξη πολιτικών στην υγεία.

1.2 Μέθοδοι

Διεξήχθη συστηματική αναζήτηση στη βάση δεδομένων PubMed για RCTs για ασθενείς πάσχοντες από σχιζοφρένια, θεραπευόμενους με ρισπεριδόνη μακράς δράσης, που δημοσιεύτηκαν μεταξύ του έτους 2002 και 2025. Η ποιότητα αναφοράς των αξιολογήθηκε με τη χρήση της λίστας 37 σημείων βάσει των επικαιροποιημένων κατευθυντήριων οδηγιών CONSORT 2010. Η συμμόρφωση ≥75% θεωρήθηκε επαρκής. Ο πρωταρχικός στόχος ήταν να υπολογιστεί η μέση συμμόρφωση με τις οδηγίες CONSORT μεταξύ των επιλεγμένων RCTs και να διεξαχθεί περαιτέρω ανάλυση της συμμόρφωσης μέσω περιγραφικών στατιστικών μεθόδων. Οι δευτερεύοντες στόχοι περιλάμβαναν την εκτίμηση της συμμόρφωσης με κάθε στοιχείο της λίστας CONSORT και την ανάλυση πιθανών παραγόντων που επηρεάζουν την ποιότητα αναφοράς —όπως ο συντελεστής απήχησης του περιοδικού, το μέγεθος δείγματος και το έτος δημοσίευσης —μέσω μονοπαραγοντικής και πολυπαραγοντικής ανάλυσης.

1.3 Αποτελέσματα

Δεκατρείς μελέτες πληρούσαν τα κριτήρια για την ένταξη στην μελέτη. Ο μέσος όρος συμμόρφωσης με τις οδηγίες CONSORT ήταν 77.34% ± 12.89% (τυπική απόκλιση). Από τις μελέτες που αξιολογήθηκαν, εννέα (69.2%) παρουσίασαν επαρκή ποιότητα αναφοράς (≥75%), ενώ τέσσερις (30.8%) χαρακτηρίστηκαν με ανεπαρκή αναφορά (<75%). Από τα 37 στοιχεία της λίστας, τα 22 αναφέρθηκαν σε τουλάχιστον 75% των μελετών. Ανιχνεύθηκε στατιστικά σημαντική συσχέτιση μεταξύ του έτους δημοσίευσης του άρθρου και της συμμόρφωσης με τις οδηγίες CONSORT (Spearman’s $\rho = 0.772$, $p = 0.002$), υποδεικνύοντας βελτίωση της ποιότητας αναφοράς με την πάροδο του χρόνου. Η μονοπαραγοντική ανάλυση δεν ανέδειξε στατιστικά σημαντική συσχέτιση μεταξύ της ποιότητας αναφοράς και των πιθανών καθοριστικών παραγόντων: συντελεστής απήχησης του περιοδικού [p=0.217, OR=10.5, 95%CI= (0.668-165.114)] ή μέγεθος δείγματος [p= 0.266, OR=6, 95%CI=

(0.422-85.248)]. Η ανάλυση λογιστικής παλινδρόμησης δεν ανέδειξε σημαντικούς προβλεπτικούς παράγοντες για την ποιότητα αναφοράς, αν και ο υψηλότερος συντελεστής απήχησης και το μεγαλύτερο μέγεθος δείγματος παρουσίασαν μη στατιστικά σημαντική τάση για καλύτερη συμμόρφωση.

1.4 Συζήτηση

Η ποιότητα αναφοράς των ελεγχόμενων τυχαιοποιημένων μελετών (RCTs) που αφορούν τη ρισπεριδόνη στη σχιζοφρένεια φαίνεται να είναι επαρκής, με γενικά καλή συμμόρφωση προς τις οδηγίες CONSORT. Επιπλέον, τα ευρήματά μας υποδεικνύουν βελτίωση αναφοράς με την πάροδο των ετών, γεγονός που καταδεικνύει τη θετική επίδραση της υιοθέτησης των οδηγιών CONSORTστη μεθοδολογία των RCTs.

Λέξεις-κλειδιά: Τυχαιοποιημένες ελεγχόμενες δοκιμές, ρισπεριδόνη μακράς δράσης, TV-46000, RBP-7000, σχιζοφρένεια, λίστα ελέγχου CONSORT

2. Introduction

Schizophrenia is widely regarded as one of the most complex and disabling of all brain diseases, characterized by a range of cognitive, behavioral and emotional dysfunctions. It affects approximately 1% of the population. It continues to be classified and diagnosed based solely on its clinical phenomenology [16], [17].

The diagnosis requires the presence of at least two core symptoms, each occurring for a significant duration within a one-month period (or less if successfully treated). At least one of these symptoms must be delusions, hallucinations, or disorganized speech. Moreover, the disorder must result in substantial impairment in at least one major domain of functioning, such as occupational performance, interpersonal relationships, or self-care [26].

Suicidal behavior is highly prevalent among individuals with schizophrenia, with approximately 25% to 50% attempting suicide and up to 10% eventually succeeding. Consequently, the mortality rate is estimated to be eight times higher than that of the general population. In the United States, the economic burden of schizophrenia, including both direct and indirect costs, is projected to reach tens of billions of dollars annually. Increasing evidence indicates that the persistence of positive symptoms accelerates the progressive loss of brain tissue associated with recurrent psychotic episodes, frequently leading to repeated hospitalizations [16].

Despite the critical role of sustained antipsychotic treatment in schizophrenia management, long term adherence to oral medication remains a significant therapeutic challenge, posing substantial barriers to effective disease control [19],[20].

Evidence suggests that the use of long-acting injectable (LAI) antipsychotic agents enhances treatment adherence in comparison to oral antipsychotics and is significantly linked to reductions in psychotic symptom exacerbations, relapse rates, and hospital readmissions [21-24].

Risperidone was the first second-generation antipsychotic to become available as a long-acting depot injection and it is currently available in various formulations designed to enhance treatment adherence and provide sustained therapeutic effects for patients with schizophrenia and related psychosis [9].

More recent innovations include subcutaneous injections, such as RBP-7000 which offer monthly dosing, without oral supplementation at initiation of treatment. TV-46000, provides flexible dosing intervals of monthly and bimonthly, according to patients needs. These developments represent significant progress in simplifying treatment regimens and improving outcomes for individuals requiring long-term antipsychotic therapy [5].

There is evidence that the quality of reporting in randomized controlled trials (RCTs) remains suboptimal, impeding the assessment of reliability, validity, and systematic review inclusion. Methodological analyses reveal that poor reporting and study design contribute to biased treatment effect estimates, undermining RCTs' value as the gold standard for evaluating interventions in medicine [15].

To address this challenge, a group of researchers and journal editors developed the CONSORT (Consolidated Standards for Reporting Trials) statement, first introduced in 1996 and later revised in 2001 and 2010. This framework includes a structured checklist and a flow diagram designed to improve the clarity and transparency in RCT reporting. Widely endorsed by leading medical journals, CONSORT facilitates critical appraisal and interpretation of trial findings [15].

The 2010 revision refined checklist wording, improved clarity, and incorporated recommendations on emerging concerns, such as selective outcome reporting bias [15].

There is limited research comprehensively assessing the quality of reporting in clinical trials in psychiatry [25].

This study aims to assess the reporting quality of RCTs on long-acting risperidone (RLAI) for schizophrenia, published between 2002 and 2025, using the CONSORT 2010 guidelines. Additionally, it seeks to identify factors influencing reporting quality, including journal impact factor, sample size, and publication year.

To our knowledge, there is no dedicated study on CONSORT compliance in long-acting injectable antipsychotic RCTs. Furthermore, this study examines reporting quality in both traditional intramuscular (IM) risperidone formulations (Risperdal Consta) and newer subcutaneous depot formulations (RBP-7000, TV-46000), providing comprehensive assessment of methodological transparency in this field.

3. Methods

3.1. Data sources and search strategies

To identify relevant randomized controlled trials (RCTs) evaluating the efficacy of long- acting risperidone in schizophrenia we searched the PubMed database using the key words: schizophrenia, psychosis, long-acting risperidone, efficacy, TV-46000, RBP-7000 from 2002 until 2025.

Our search was conducted in English literature and "humans" as a filter for species.

The following query was used:

("schizophrenia" OR "psychosis")

AND ("long-acting risperidone" OR "TV-46000" OR "RBP-7000")

AND ("efficacy")

AND ("randomized controlled trial" OR "RCT")

AND (2002:2025[dp])

AND (english[lang])

3.2. Eligibility of studies

We used the PICO (Population, Intervention, Comparison, Outcome) framework to structure our research question and guide the selection of studies.

Eligibility criteria:

- Population: Adults (≥18 years old) diagnosed with schizophrenia according to ICD-10, DSM-V or DSM-IV criteria
- Intervention: Long-acting risperidone, with any comparison group considered.
- Outcome: Clinical response measured by reduction in PANSS scale.

Excluded:

- Literature reviews
- Open-label, non-randomized studies
- Pharmacokinetic and tolerability studies
- Long-term safety, tolerability and effectiveness studies
- Observational non-interventional studies
- Studies involving patients with co morbid substance or alcohol use disorders
- Systematic reviews
- Meta- analyses
- Studies published after 2005 that do not report a trial registration number[18]
- Studies measuring treatment effect using imaging techniques (e.g. MRI-based assessments)
- Relapse prevention studies

3.3. Reporting assessment tool

We used the revised CONSORT checklist, which includes a 37-item questionnaire. The CONSORT explanation and elaboration document was used as guidance for our process. CONSORT provides instructions for every section of an RCT article (title,

introduction, methods, results and funding) and covers every aspect of a well-conducted clinical trial.

3.4. Methodological evaluation

Each selected article was evaluated during the review process. Each item was scored as follows: “yes”, worth one (1) point when accurately reported; “no” or unclear, scoring zero (0) points for incomplete or absent reporting. An item was considered a positive response if it was mentioned in a different section. Items market as “when applicable”(7b), “if done”(11a), or “if relevant” in the CONSORT checklist were scored as “non-applicable” only when it was clear that the item was either irrelevant to the study or did not require explicit reporting. This resulted in a score range from 0 to 37.

Additional details included the publication year, the journal ranking (Journal Impact Factor- IF), the name of the first author, the sample size and the year of publication.

3.5. Outcome measures and Statistical analysis

The primary outcome measure was the mean CONSORT adherence of RCTs for long-acting risperidone in schizophrenia. The cut-off point for mean compliance was set at a value greater or equal to 75%. The identification of potential factors contributing to the reporting quality of RCTs and the calculation of compliance per CONSORT item were the secondary objectives of our study. All parameters were firstly analyzed as categorical variables: IF (<5.9, ≥ 5.9 based on the median of our sample), sample size (<452, ≥ 452 based on the median of our sample).

Univariate analysis was conducted using the Pearson’s chi-square test (Fisher's exact test was applied if the expected values in any of the cells were less than 5). A p-value of 0.20 was arbitrarily set as the cut-off value for entry into logistic regression. A significance level of 0.05 was established as the threshold for statistical significance.

Odds ratios (ORs), 95% confidence intervals (95% CIs), and p-values are presented. Spearman's correlation coefficient was performed to examine potential linear correlations between IF, publication year and reporting quality. All statistical analyses were conducted using IBM SPSS Statistics Software v.29.

4.Results

PubMed search yielded 81 articles published from 2002 to 2025. Following the initial screening of titles and abstracts, 24 full texts were reviewed. Among them 13 articles were considered eligible for the review.

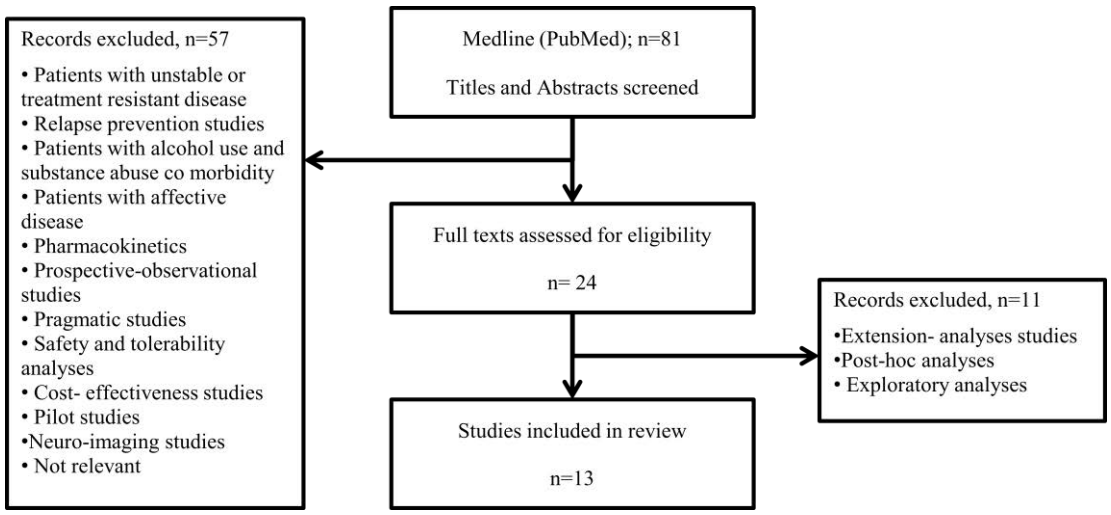

Figure 1. Flow chart of the literature search.

4.1.Consort adherence

The mean compliance was 77.34 % with SD=12.89%. The median value was 81,01%. The minimum and the maximum compliance were 54.05% and 94.59%, respectively. Among the studies 9 (69,2%) registered a good reporting quality (≥75% of the items), while 4 (30.8%) presented with suboptimal reporting (<75% of the items). The mean proportion of adherence to the CONSORT statement for each study is presented in Table 1.

Table 1. List of RCTs along with the CONSORT score**.**

Article	Medical Journal	Year	Mean compliance score (%)
Kane et al.	Am J Psychiatry	2003	59.45
Chue et al.	European neuro-psychopharmacology	2005	62.16
Bai et al.	Pharmacopsychiatry	2006	54.05
Keks et al.	British Journal of Psychiatry	2007	78.37
Gaebel et al.	Neuropsychopharmacology	2010	81.08
Li et al.	Progress in Neuro-Psychopharmacology &	2011	78.37

	Biological Psychiatry		
Pandina et al.	Progress in Neuro-Psychopharmacology & Biological Psychiatry	2011	86.48
Rosenheck et al.	The New England Journal of Medicine	2011	86.48
Covell et al.	J Clinical Psychiatry	2012	64.86
Fleischhaker et al.	International Journal of Neuropsychopharmacology	2012	89.19
Nasser et al.	Journal of Clinical Psychopharmacology	2016	83.78
Correll et al.	NPJ Schizophrenia- Nature partner journals	2020	86.49
Kane et al.	The Lancet Psychiatry	2023	94.59

Compliance per CONSORT item is presented at figure 2 and table 1.

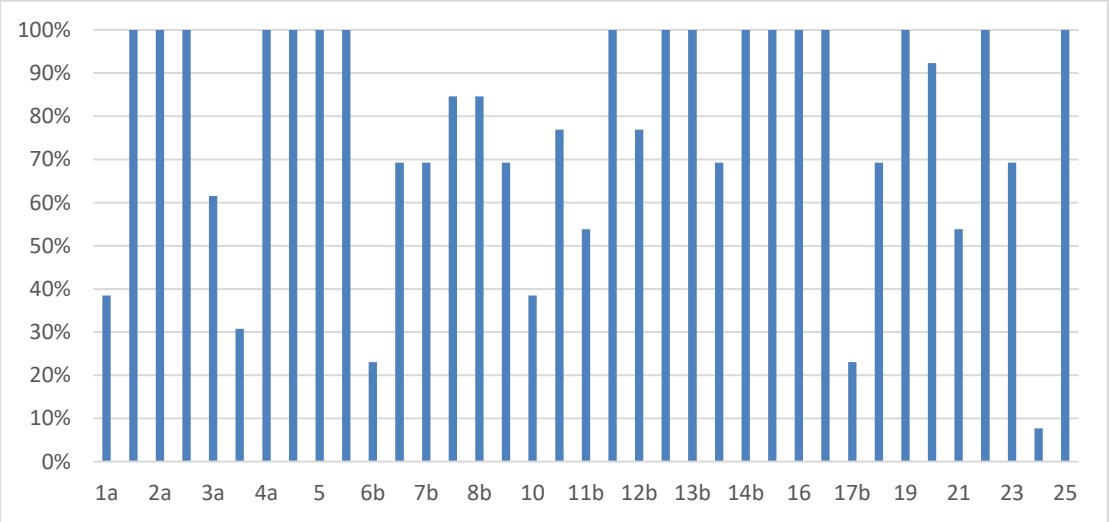

Figure 2. Graphical presentation of adherence per Consort item.

Out of the 37 items on the checklist, 22 were reported with at least 75% compliance across the studies, while 17 items were consistently reported in all (100%) of the publications. The items that were mostly underreported were 1a, 3b, 6b, 9, 10, 11b, 17b, 21 and 24.

Table 2. Compliance per Consort item

Category	Description	Compliance
1a	5	0.38
1b	13	1.00
2a	13	1.00
2b	13	1.00
3a	8	0.62
3b	4	0.31
4a	13	1.00
4b	13	1.00
5	13	1.00
6a	13	1.00
6b	3	0.23
7a	9	0.69
7b	9	0.69
8a	11	0.85
8b	11	0.85
9	9	0.69
10	5	0.38
11a	10	0.77
11b	7	0.54
12a	13	1.00
12b	10	0.77
13a	13	1.00
13b	13	1.00
14a	9	0.69
14b	13	1.00
15	13	1.00
16	13	1.00
17a	13	1.00
17b	3	0.23
18	9	0.69
19	13	1.00
20	12	0.92
21	7	0.54
22	13	1.00
23	9	0.69
24	1	0.08
25	13	1.00

4.2 Determinants of reporting quality

We examined the association between adequate reporting, defined as CONSORT compliance of ≥75%, and two categorical variables: Journal impact factor (≥5.9 vs. <5.9, based on the median of our sample) and sample size (≥452 vs.<452, based on

the median of our sample). Pearson's chi square was used to assess statistical significance, and Fisher's exact test was applied when expected cell counts were less than 5. No statistically significant correlations were identified for either Journal impact factor (p=0.217) or sample size (p=0.266).

Table 3. Univariate analysis of possible determinants of reporting quality

Parameter	OR	95% CI	p-value
Impact factor ≥ 5,9	10.5	0.668-165.114	0.217
Sample size ≥ 452	6.00	0.422-85.248	0.266

Additionally, we examined the impact factor as a continuous variable, allowing us to evaluate any potential linear relationships between the impact factor and the reporting quality. The range of journal impact factors in our study was 2.9 to 96.2.

Table 4. List of journal impact factors along with the CONSORT score

Medical Journal	Impact Factor	Mean compliance score (%)
Am J Psychiatry	15.1	59.45
European neuro-psychopharmacology	6.1	62.16
Pharmacopsychiatry	3.6	54.05
British Journal of Psychiatry	8.7	78.37
Neuropsychopharmacology	6.6	81.08
Progress in Neuro-Psychopharmacology & Biological Psychiatry	5.3	78.37
Progress in Neuro-Psychopharmacology & Biological Psychiatry	5.3	86.48
The New England Journal of Medicine	96.2	86.48
J Clinical Psychiatry	5.9	64.86
International Journal of Neuropsychopharmacology	4.8	89.19
Journal of Clinical Psychopharmacology	2.9	83.78
NPJ Schizophrenia- Nature partner journals	5.7	86.49
The Lancet Psychiatry	30.8	94.59

A Spearman correlation analysis was performed. The analysis did not reveal statistically significant correlation between the journals' impact factor and reporting quality scores of the RCTs (Spearman's Correlation ρ= 0.09, p-value= 0.763).

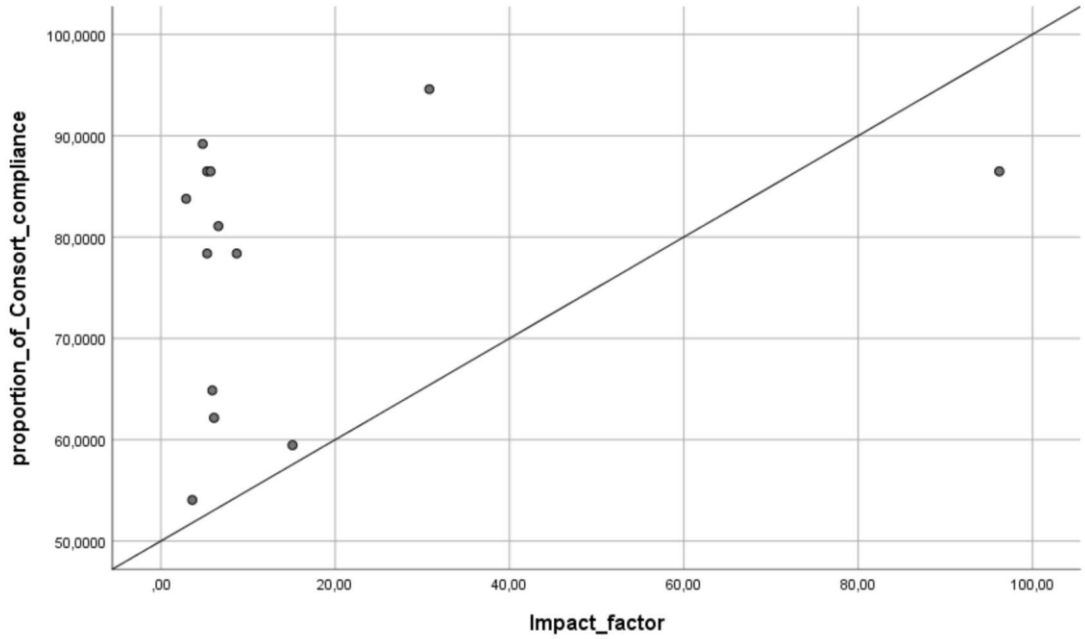

Figure 3. Correlation (scatter- plot) between Impact factor and reporting quality

We further examined the relationship between the publication year of the RCTs and the CONSORT scores to investigate potential trends in reporting quality over time. Our findings revealed statistically significant relationship (Spearman's Correlation ρ=0.772, p-value= 0.002).

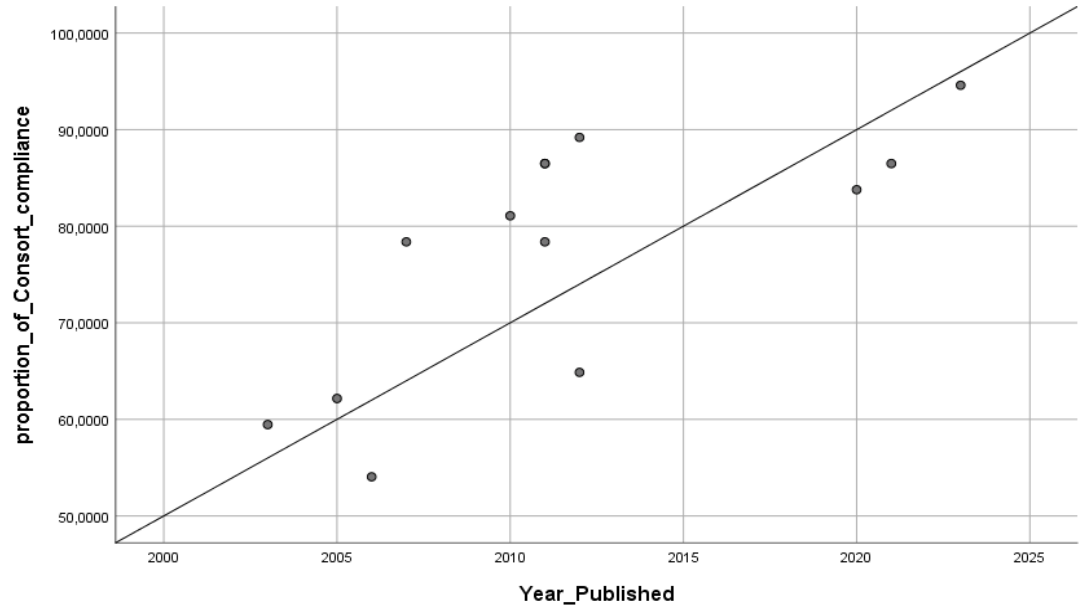

Figure 4. Correlation (scatter-plot) between Year of publication and reporting quality

This indicated a strong positive correlation between the proportion of CONSORT compliance and the year of publication. As the year of publication increases, adherence to the CONSORT guidelines tends to improve.

Binary logistic regression reports that (Table 5) Impact factor has the highest impact on the prediction model [Exp(B)= 9.818], however, it failed to determine statistical significance for each of the independent variables: Impact factor (p=0.129) and Sample size (p=0.265).

Table 5.Multivariate analysis of possible determinants of reporting quality

Parameter	OR – Exp(B)	95% CI	p-value
IF of Journal	9.818	0.513-187.726	0.129
Sample Size	5.501	0.274-110.253	0.265

5.Discussion

In this study, 13 eligible RCTs on long-acting risperidone in schizophrenia were assessed for adherence to CONSORT guidelines. The findings indicate that reporting quality is generally adequate with mean CONSORT compliance of 77.34%. Notably, reporting quality has improved over time, as evidenced by the statistically significant correlation between publication year and CONSORT adherence (Spearman's ρ=0.722, p=0.002), a finding consistent with previous research (Han et al., 2012).

However, no significant associations were found between reporting quality and potential determinants such as journal impact factor and sample size, despite non-significant trend suggesting that higher-impact journals and larger studies may demonstrate better adherence.

Despite the overall improvement in reporting quality, persistent gaps remain, particularly in key CONSORT checklist items. The absence of explicit RCT identification in titles (Item 1a, reported in only 38% of studies) and underreported changes in methodology (Item 3b, 31%) poses challenges to trial visibility and transparency [15]. Additionally, poor reporting of allocation concealment (Item 9, 69%) and intervention similarity (Item 11b, 54%) raises concerns regarding selection and performance biases. Ensuring all trials are prospectively registered and their protocols are publicly available would enhance reproducibility in psychiatric clinical trials.

This study is subject to some limitations, most notably the relatively small number of studies included, which may restrict the generalizability of findings.

In conclusion, these findings underscore the need for stricter journal enforcement of CONSORT guidelines and further investigation into additional factors influencing reporting quality.

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