Original

Juan P. Carrasco-Picazo[1]

Aurora González-Teruel[2]

Ana M. Gálvez-Llompart[1]

Juan A. Carbonell-Asins[3]

Miguel Hernández-Viadel[1-4]

Pain sensitivity in patients with schizophrenia: a systematic review and meta-analysis

[1] Department of Psychiatry, Clinical Hospital of Valencia, Valencia, Spain.

[2] Department of History of Science and Documentation, School of Medicine, University of Valencia, Valencia, Spain.

[3] Biostatistician. Bioinformatics and Biostatistics Unit. Biomedical Research Institute INCLIVA. Valencia, Spain

[4] Department of Clinical Medicine, School of Medicine, University of Valencia, Spain.

ABSTRACT

Background. Alterations in pain perception have been observed in people diagnosed with schizophrenia. Some research suggests the existence of a possible hyposensitivity, while others describe a hypersensitivity to pain in people with schizophrenia. In summary, the studies present contradictory results.

Methods. A systematic review of experimental and comparative studies has been conducted in 5 different databases, including those studies that measure pain experimentally inducing it with physical methods and that compares the results with a healthy control group. Afterwards, a meta-analysis was carried out comparing the patients with schizophrenia to the healthy controls, using the random effects model.

Results. Nine studies were finally selected, with a total of 186 participants diagnosed with schizophrenia and 186 healthy controls. In the meta-analysis, no significative differences were observed in the general analysis. But when the type of stimuli was studied separately (mechanical, thermal, or electrical), significative differences in favor of a higher sensitivity in the patients with schizophrenia were observed in the studies that measured pain with mechanical pressure or ischemia, not in those that used thermal or electrical methods.

Conclusions. The global result of our systematic review does not support the existence of an alteration in pain sensitivity in subjects with schizophrenia, although a subgroup analysis suggests that when pain stimulation is caused by mechanical methods, people with schizophrenia present hypersensitivity to pain compared to healthy controls. Although these results are novel data, more studies are required to replicate these results.

Keywords. Schizophrenia, Experimental pain, Pain tolerance, Pain perception, Pain threshold, Pain assessment.

Actas Esp Psiquiatr 2023;51(1): 29-40 | ISSN: 1578-2735

SENSIBILIDAD AL DOLOR EN PACIENTES CON ESQUIZOFRENIA: UNA REVISIÓN SISTEMÁTICA Y METAANÁLISIS

RESUMEN

Introducción. En personas diagnosticadas de esquizofrenia se han observado alteraciones en la percepción del dolor. Algunas investigaciones sugieren la existencia de una posible hiposensibilidad, mientras que otras describen una hipersensibilidad al dolor en personas con esquizofrenia. En definitiva, los estudios presentan resultados contradictorios.

Método. Se ha llevado a cabo una revisión sistemática de estudios experimentales y comparativos en 5 bases de datos diferentes, incluyendo aquellos estudios que evalúan el dolor inducido de manera experimental mediante métodos físicos y comparando los resultados con un grupo control sano. Posteriormente, se ha llevado a cabo un metaanálisis comparando los pacientes con esquizofrenia con los controles sanos, utilizando un modelo de efectos aleatorios.

Resultados. Finalmente fueron seleccionados nueve estudios, con un total de 186 participantes diagnosticados de esquizofrenia y 186 controles sanos. En el metaanálisis no se observaron diferencias significativas en la comparación de análisis general entre pacientes con esquizofrenia y controles

Corresponding author

Miguel Hernández-Viadel

complete address: Department of Psychiatry, Clinical Hospital of Valencia, Blasco Ibañez Avenue nº 17, 46010-Valencia (Spain)

e-mail address: Miguel.Hernandez-Viadel@uv.es

sanos. No obstante, cuando el tipo de estímulo fue estudiado por separado (mecánico, térmico o eléctrico), se observaron diferencias significativas a favor de una mayor sensibilidad al dolor en los pacientes con esquizofrenia en los estudios que evaluaron el dolor con presión mecánica o isquemia, pero no en aquellos que utilizaron métodos térmicos o eléctricos.

Conclusiones. El resultado global de nuestra revisión sistemática no respalda la existencia de una alteración en la sensibilidad al dolor en los sujetos con esquizofrenia, aunque un análisis de subgrupos sugiere que cuando el estímulo del dolor es causado por métodos mecánicos, las personas con esquizofrenia presentan una hipersensibilidad al dolor en comparación con los controles sanos. Aunque estos resultados son datos novedosos, se requieren más estudios para replicar los resultados.

Palabras clave. Esquizofrenia, Dolor Experimental, Tolerancia al Dolor, Percepción del Dolor, Umbral del dolor, Evaluación del dolor.

INTRODUCTION

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage"[1]. Furthermore, pain is a personal experience and is always influenced by biological, psychological, and social factors[1].

In the latest revision of the definition of pain, the IASP points out the relevance of psychological aspects among the components of pain. The reality is that emotions can produce biological and neuroinflammatory changes involved in pain pathways[2]. Neuroimaging studies have shown that sensory, affective, and cognitive regions interact with each other to determine the final experience of pain[3].

Pain perception is influenced by age, gender, and culture, but also by psychological and emotional factors such as anxiety, pain-related fear, depression, anger, and positive emotions. On the other hand, the perception and experience of pain are also influenced by cognitive factors, such as attention, expectations, and pain assessment[3].

For decades, alterations in the perception of pain in people diagnosed with schizophrenia have been observed and studied[4-6]. Classical authors such as Kraepelin[7] and Bleuler[8] have already described how these patients "often become less sensitive to bodily discomforts" and exemplify some behaviors that demonstrate this, like those we frequently find in daily clinical practice. For example, people with schizophrenia who self-injure or delay their attention in the medical service when they suffer from pathologies that cause pain[9-10].

Despite the methodological difficulties to measure pain objectively, in recent years various studies have been carried out on the relationship between schizophrenia and pain. On the one hand, there are numerous studies that suggest the existence of an increase in the pain threshold or a decreased sensitivity to pain in people with schizophrenia compared to healthy subjects[5,6,11-14]. On the other hand, several studies show an increase in sensitivity to pain in people with schizophrenia[15-17]. Finally, there are also studies in which no relationship is found between schizophrenia and pain threshold[18-21].

To give a logical explanation for this disparity in results, it has been suggested that schizophrenia would be associated with decreased pain sensitivity only when subjective methods are used to assess pain, while there would be no abnormalities in the physiological response[22]. It has also been suggested that, regardless of the pain threshold, the reason why patients with schizophrenia do not recognize and report pain is due to cognitive deficits associated with their pathology[23].

Some characteristic symptoms of schizophrenia, such as affective flattening, attention deficit or the presence of sensory-perceptive alterations, could affect the way pain is experienced or expressed and have been associated with hyposensitivity to pain. The neural pathways that process the dimensions that make up pain (sensory-discriminative, motivational-affective, and cognitive-evaluative) could be affected differently in schizophrenia, leading to different outcomes depending on which aspect of pain is primarily assessed. For example, a decrease in the experience of pain could be due to altered processing of the motivational-affective aspect of pain due to frontal lobe dysfunction in schizophrenia[23]. Other authors[24] suggest that the apparent insensitivity to pain reported in schizophrenia would be more related to a different way of expressing pain than to real endogenous analgesia. Lack of social skills and deficits in language and communication could influence both the verbal and non-verbal expression of pain in people with schizophrenia.

In the study of the association between pain and schizophrenia, two main approaches can be recognized: clinical pain and experimental pain. Clinical pain is that which occurs naturally and not provoked under experimental conditions. This type of pain is important because it often leads people to seek medical help and can be the basis for a serious medical condition (eg, appendicitis, acute myocardial infarction).

Actas Esp Psiquiatr 2023;51(1): 29-40 | ISSN: 1578-2735

The study of the association between clinical pain and schizophrenia has generated diverse results. In the review by Engels et al.[23], the prevalence and intensity of clinical pain caused by an apparent medical cause (eg, lumbar puncture or myocardial infarction) is lower in subjects with schizophrenia compared to healthy controls. However, when studying the prevalence of clinical pain, without medical intervention (eg, headache), the results suggest that there are no differences between subjects with schizophrenia and controls. The meta-analysis of clinical pain studies by Stubbs et al.[24] coincides with these findings, finding no differences in the prevalence of clinical pain between subjects with schizophrenia and the control group.

On the other hand, pain perceived under certain experimental conditions has also been studied. Stubbs et al.[11] in their systematic review and meta-analysis of experimental studies found that subjects with schizophrenia had a higher pain threshold and tolerance than healthy controls. These results are in line with those found by Potvin and Marchand[22], who demonstrated a decreased response to experimentally induced pain in subjects with schizophrenia compared to controls.

There were no differences if the patients were prescribed antipsychotic treatment or not. However, later published studies have found different results. Paquet et al.[16,19] described hypersensitivity to pain in subjects with schizophrenia compared to healthy controls, and Duval et al.[18] found no differences between the two groups.

Given the lack of conclusive results, with studies that obtain contradictory results, we consider it necessary to carry out a review that allows us to know the most recent scientific evidence on pain tolerance in patients with schizophrenia compared to healthy people or with another mental disorder.

METHOD

This systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[26] guidelines. The protocol was registered in the PROSPERO database under registration number CRD42021232874.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) any type of experimental study assessing pain response in subjects with schizophrenia compared to the control group; (2) participants were persons older than 16 years diagnosed with schizophrenia according to DSM[27] or ICD[28] criteria. If there were multiple diagnoses in the sample, at least 50% of the patients had to be diagnosed with schizophrenia; (3) that included a clear and measurable assessment of the pain response of the individuals participating in the study; (4) published in English, Spanish, French, Italian or Portuguese.

Exclusion criteria were as follows: (1) Studies other than experimental studies or not reporting comparative data with respect to a control group; (2) Patients with a diagnosis other than schizophrenia; (3) Patients under 16 years of age; (4) Studies in which the method used to measure pain intensity was not clearly stated.

Sources of information and search strategy

Five complementary databases were used to obtain relevant papers: PubMed, Embase, PsycINFO, Web of Science-Core Collection, both the Science Citation Index and the Social Science Citation Index (WoS-SCI / SSCI) and Scopus. The search strategies for each of them (Annex I) were constructed on the basis of the concepts Schizophrenia and Pain. In PubMed and Embase the search was carried out based on the Mesh and Emtree descriptors, as well as in the title and abstract fields. In PsycINFO in the subject, title, and abstract fields. In the case of WoS-SCI / SSCI and Scopus the search was carried out in the title, abstract and keyword fields. In Embase as well as in WoS-SCI / SSCI and Scopus, limits were applied for the selection of articles and reviews only. In PsycINFO the search was limited to peer-reviewed papers. The search and download of bibliographic records were performed by a researcher (AGT) in December 2020, with results limited to the period 2011 onwards. This year (2011) was chosen to provide data from the last 10 years that can add more up-to-date information to revisions from previous years.

Selection process

Once duplicate bibliographic records were removed, two authors (AMGL and JPCP) independently reviewed the title and abstract of each record for relevance. This process resulted in a 99.2% concordance, and discrepancies were resolved by consensus. Subsequently, from the records initially considered relevant, the full text was obtained and reviewed by two authors independently (AMGL and JPCP). Discrepancies regarding inclusion or non-inclusion were resolved by arbitration by a third author (MHV).

Data analysis

Four authors analysed the following aspects of each study: territorial scope and sample size of the study, characteristics of the participants (age, diagnostic manual

used, patients admitted to hospital or under outpatient follow-up, with or without antipsychotic medication), type of stimulus causing pain (mechanical, thermal, electrical), modality of pain studied (sensory threshold, pain threshold, pain tolerance), instrument used to measure pain, and main results. One author (MHV) checked the analysis to assess consistency between researchers. Discrepancies were resolved by consensus.

Assessment of study quality

The quality of individual papers was assessed using the Newcastle-Ottawa Scale (NOS) used in systematic reviews for the evaluation of interventions including non-randomised studies[29].

Assessment of publication bias

Publication bias was examined visually using the funnel plot showing effect size versus standard error. In addition, Egger's test was performed to test the hypothesis of symmetry in the funnel plot.

Statistical analysis

A meta-analysis was performed by pooling articles to assess pain sensitivity in subjects with schizophrenia compared to healthy controls. This pain sensitivity was measured with the mean in the schizophrenia-diagnosed group and in the control group with scales to assess pain sensitivity. Total heterogeneity was studied using the I2 index based on a chi-square test. It was agreed to use the random effects model in case of a Cochran's Q test <0.05 or an I2 index higher than 50%.

Given the different types of methods used to produce the painful stimulus, it was also decided to perform a meta-regression to study the effect on pain sensitivity according to the administration of each method. All analyses were performed in R (version 3.6.2).

RESULTS

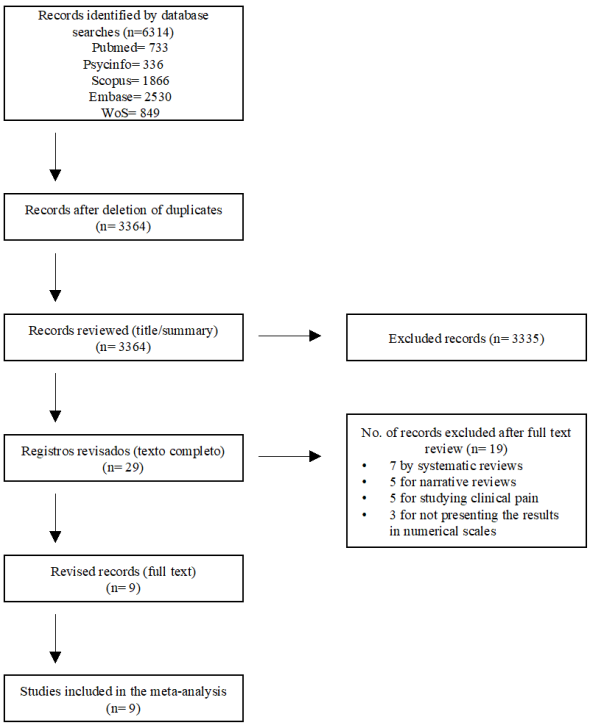
Selection of studies

Figure 1 presents the selection process of the studies included in the review.

Characteristics of the included studies

Of the 9 studies, 4 were conducted in France[16-18,25]. The other 5 were conducted in Germany[12], Mexico[28], Canada[15], Italy[13] and China[29] respectively (Table 1). A total of 186 participants diagnosed with schizophrenia and 186 controls were studied, with a mean age ranging from 18 to 66 years.

Figure 1 Flow chart of the selected studies.



Regarding the clinical characteristics of the patients, 7 studies included participants diagnosed with schizophrenia in a stable phase of the illness, 1 in a decompensation phase according to the PANSS scale and 1 did not include information on clinical status. All patients were recruited in an outpatient setting and all but 2 patients in one of the studies[18] were under stable neuroleptic treatment.

Among the different ways of studying pain, 4 studies were conducted by thermal stimulation (two of them by laser and 2 by heat and cold sources), 3 by mechanical stimulation (applying pressure and ischaemia to the extremities) and 2 by electrical stimulation.

To assess participants' pain tolerance, 2 of the studies used the visual analogue scale (VAS) from 0 to100, 4 the VAS scale from 0 to 10, 2 the numerical rating scale (NRS 0-10) and 1 a verbal numerical scale 1-10. All the scales use the same method for the patient to express the subjective pain they feel visually or verbally. Transforming all results to a scale of 0-10, the values ranged from 2.23 to 7.08 in the group of patients diagnosed with schizophrenia and from 1.08 to 6.54 in the control group.

Actas Esp Psiquiatr 2023;51(1): 29-40 | ISSN: 1578-2735

Table 1 Study characteristics

Study	Country	Type of stimulus	Sample (n)	Anti-psychotic treatment	Clinical scales (mean)	Variable used	Measuring instrument	Magnitude (mean difference)	Results	NOS
Minichino, 2016 [13]	Italy	Laser (Thermal)	SCH 20 HC 19	Yes	PANSS 36.7 ±8.4	Pain threshold	mJ/mm2 NRS (0-10)	PTh (mJ/mm2) SCH 76.4 (21.1) vs HC 62.6 (18.9) NRS: SCH 3,5 (2,1) vs HC 6,0 (1,3)	High pain threshold in schizophrenia	4
Paquet, 2017[16]	France	Mechanical (Pressure, Ischaemia)	SCH 30 HC 30	Yes	No information	Pain threshold and pain intensity	VAS (0-10)	VAS SCH 2,8 (3,2) vs HC 1,2 (1,3)	Hypersensitivity in schizophrenia	6
Paquet 2019[25]	France	Mechanical (Pressure, Ischaemia)	SCH 17 HC 16	Yes	No information	Pain threshold and pain intensity	VAS (0-10)	VAS for 160 KPaSCH 2,35 (1,77) vs HC 1,08 (1,16)	Hypersensitivity in schizophrenia	6
Duval, 2016[18]	France	Electrical stimulation	SCH 21 HC 21	19 patients yes, 2 no	PANSS 77.6± 10.1	Pain threshold and pain intensity	VAS (0-100)	VAS for pain intensity at 1300 mAmp SCH 22,35 (22,06) vs HC 13,52 (17,93) VAS for pain intensity at 1800 mAmp SCH 31,10 (28,3) vs HC 18,13 (22,71)	No difference	4
Zhou, 2019[29]	China	Laser (Thermal)	SCH 21 HC 21	Yes	PANSS 55.3 ± 12.9	Pain threshold and pain intensity	NRS (0-10)	NRS (0-10) SCH 3,7 (1,4) vs HC 5,4 (1,5)	Hyposensitivity in schizophrenia	5
Lévesque, 2012[15]	Canada	Electrical stimulation	SCH 12 HC 11	Yes	PANSS 64.67 ±3.69	Pain threshold	Motor réflex NRS (0-10)	Verbal scale (0-10) Low frequency SCH 3.78 (0,70) vs HC 2.79 (0.57) High frequency SCH 5.3 (0,82) vs HC 5.24 (0.81)	Low pain threshold (acute pain) Less sensitivity to prolonged pain.	5
De la Fuente -Sandoval 2010[28]	Mexico	Thermal (Heat, Cold)	SCH 12 HC 13	Yes	CGI score <2	Pain tolerance	fMRI VAS	VAS SCH 7.08 (1.62) vs HC 6.54 (1.8)	No difference	5
Girard 2011[17]	France	Mechanical (Pressure, Ischaemia)	SCH 35 HC 35	Yes	SAPS 36.3±18.4 SANS 39.9±11.5	Pain tolerance	VAS	VAS SCH 3'6(2'9) vs HC 1'4(1'6)	Hypersensitivity in schizophrenia	6
Boettger 2012[12]	Germany	Thermal (Heat , Cold)	SCH 18 HC 18	Yes	PANSS=86 SAPS=43 SANS=38	Pain tolerance	Temperature (ºC) VAS (0-100)	VAS SCH 29,3 (5,0) vs HC 35,7 (3,9)	No difference	6

SCH: People with schizophrenia, HC = Healthy controls // VAS= Visual Analogue Scale, NRS= Numerical evaluation scale // PANSS= Positive and negative symptom scale
CGI= Clinical Global Impression // SAPS= Positive Symptom Rating Scale // SANS= Negative Symptom Rating Scale
PTh= Pain perception threshold // NOS= Newcastle-Ottawa Scale// fMRI= Functional Magnetic Resonance Imaging

Differences in pain perception in schizophrenia

Of the 9 selected studies (Table 1), 6 found differences in pain perception when comparing patients with schizophrenia with the control group. Three of them concluded that patients with schizophrenia had hypersensitivity to pain, 2 found hyposensitivity or a higher pain threshold, and 1 of them had mixed results, with a lower pain threshold in acute pain and a lower sensitivity to prolonged pain.

Regarding the type of pain stimulus applied, the 3 studies that showed hypersensitivity were conducted with mechanical stimuli, the 2 studies that showed hyposensitivity were conducted with laser thermal stimulation, and the study with mixed results was conducted with electrical stimulation. Of the 3 studies that showed no difference, one

was performed with electrical stimulation and the other two with thermal stimulation without laser.

The estimated point difference in pain intensity for each study and the total result of the meta-analysis, comparing the group of patients with schizophrenia versus the group of people without schizophrenia, is shown in figure 2. For this, studies with scales between 0-100 were transformed to a 0-10 scale. Information on the pain intensity score results (mean and standard deviation) in the studies of Duval (2016) and Paquet (2019) was provided personally by the authors. The I2 index is greater than 50% and the heterogeneity between studies is significant ($p < 0.01$), so the random-effects model was used.

The result of using pooled data from the 9 studies shows no evidence of differences in the perception of pain intensity between people with schizophrenia and healthy controls (standardized mean difference: 0.23, 95% confidence interval: -0.35, 0.81).

Table 2 presents the results obtained by subgroups according to the type of method used to provoke pain. Looking at the confidence interval, the mechanical method (0.79; CI 0.41, 1.18) is the only one that does not include 0, suggesting that patients with schizophrenia would be hypersensitive to pain compared to healthy patients. That is, there would be a group effect and the results would depend on the method used ($p = 0.002$).

The assessment of risk of bias in the included studies, as mentioned above, was assessed using the Newcastle-Ottawa Scale (NOS). The results of the categorisation of each trial are presented in Table 1 (Supplementary Material 3).

Figure 2 Forest plot of the included studies

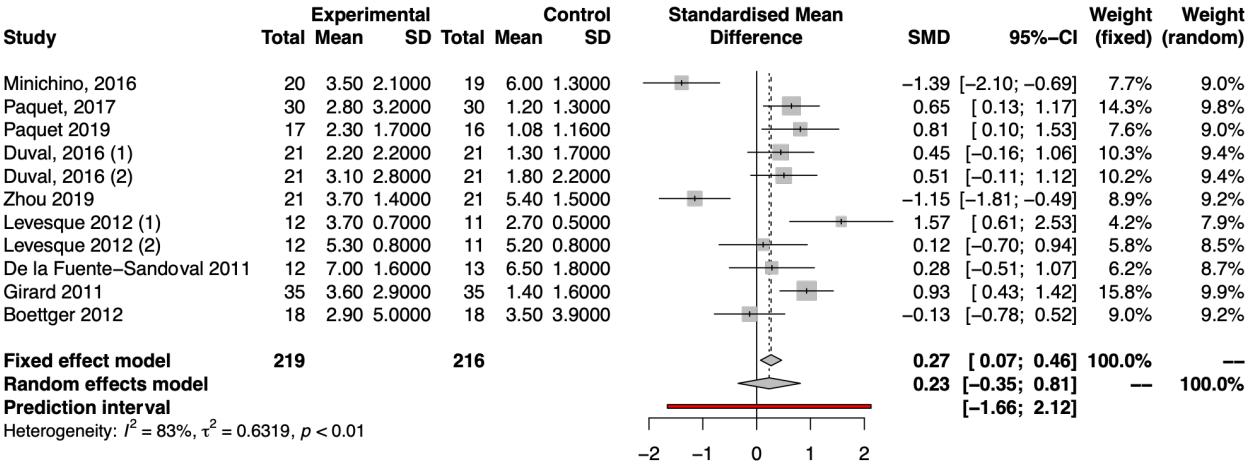


Table 2. Results by subgroups.

```
Results for subgroups (random effects model):
                    k     SMD            95%-CI  tau^2    tau     Q   I^2
Thermal method      4 -0.6087 [-1.8766; 0.6592] 0.5013 0.7080 14.25 78.9%
Mechanical method   3  0.7983 [ 0.4151; 1.1815] 0.0033 0.0578  0.60  0.0%
Electrical method   4  0.6135 [-0.3061; 1.5331] 0.2307 0.4804  5.55 45.9%

Test for subgroup differences (random effects model):
                    Q d.f. p-value
Between groups  12.03    2  0.0024
```


Actas Esp Psiquiatr 2023;51(1): 29-40 | ISSN: 1578-2735

Figure 3 | **Funnel plot for the selected studies**

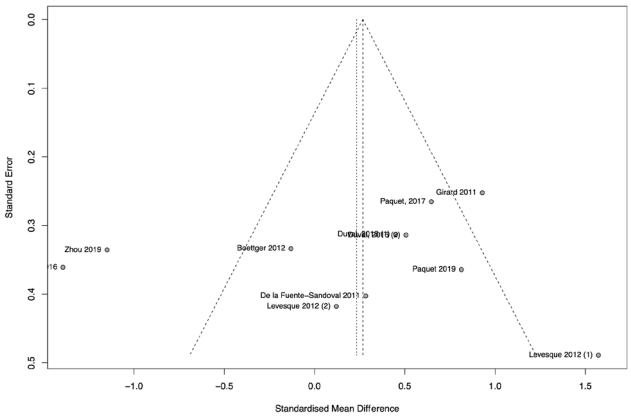


Figure 3 shows the funnel plot associated with the 9 included studies to analyse possible publication bias. Visually, it can be seen that the point cloud is symmetrically distributed around the overall effect estimate. Egger's test studies the asymmetry of the funnel plot and is used to establish whether or not there has been publication bias. According to the results obtained (p = 0.628), there is no asymmetry and, therefore, no evidence of publication bias.

DISCUSSION

In this systematic review and meta-analysis, 9 studies were identified that focused on comparing differences in pain sensitivity between patients diagnosed with schizophrenia and healthy controls. No significant differences in outcomes were obtained when comparing pain sensitivity between patients diagnosed with schizophrenia and healthy controls. However, when performing a subgroup analysis, different results were obtained for the first time depending on the type of pain stimulus. In studies where the pain stimulus was mechanically provoked, patients with schizophrenia showed a hypersensitivity to pain compared to healthy controls. This represents a novelty in the study of pain sensitivity in people with schizophrenia. There are several possible explanations for this phenomenon. One of them could be related to the fact that the method of pain generation by mechanical pressure generates more stress in patients with schizophrenia than in controls and this increases the subjective sensation of pain. On the other hand, a greater neurochemical susceptibility to mechanical pressure pain could also explain these results. However, there is not enough information to establish a clear cause and these results should be taken with caution as they are based on only 3 investigations[16,17,25] and therefore more studies are needed to replicate these results.

These results are different from those published by two previous meta-analyses[11,22] which did find significant differences in favour of increased pain tolerance and hyposensitivity in patients with schizophrenia. Stubbs et al.[11] included 17 studies, of which four have also been included in our meta-analysis, those published between 2010 and 2015. However, Stubbs' meta-analysis[11] did not perform a sub-analysis by stimulus type, and almost all of the included studies (15 out of 17) were conducted with electrical and thermal stimuli. This fact could explain the differences found with our work. On the other hand, in the meta-analysis by Potvin et al[22], 12 studies were included, the majority (11 of them) also using electrical or mechanical stimulation, finding very similar results to the study by Stubbs[11]. It is interesting to note that both meta-analyses performed a sub-analysis comparing patients with and without antipsychotic treatment, obtaining no differences between the two groups and attributing the hyposensitivity found to the disease itself.

These and previous reviews[31-33,] although they have found significant differences, highlight that the results of the studies are generally contradictory. This may be justified by differences in the design of the studies, in the different types of pain stimuli applied, in the objective of the work and in the instrument used to measure pain. In addition, the stage of the disease at the time of the patient's study and the predominance of positive or negative symptoms may also lead to some interference with the results.

Vaughan et al.[31] also highlighted similar difficulties and limitations in their work. In their review they included 11 studies comparing healthy controls with people with schizophrenia. In most of the studies in which pain threshold was measured with thermal and electrical methods, patients showed hyposensitivity to pain. In the only study included in the review and conducted with mechanical methods, they found hypersensitivity[17].

The review by Sakson-Obada[32] included 16 studies using different control groups (healthy controls, inpatients, or outpatients with other diagnoses). In this work, as in Vaughan's review[31], the use of electrical and thermal methods to provoke painful stimuli suggests the existence of hyposensitivity in people with schizophrenia compared to the control group. The authors mention that, although the results are consistent, given the scarcity of studies using other methods (compression, pinching, laser), this hyposensitivity should be considered with caution.

Given the results of our work and other studies, it is interesting to note that pain perception and tolerance may differ according to the type of stimulus used. However, given the large heterogeneity in methodology and the small

sample size of the studies, often less than 20 patients, it would be necessary to replicate these results with larger samples and to increase the number of studies in this area.

In this sense, many unknowns remain to be resolved. On the one hand, physiological and neurological changes in pain perception and response, as Sakson-Obada[32] points out, could reveal the underlying biological process and differences in pain sensitivity in patients with schizophrenia. On the other hand, as suggested by Stubbs et al[11], how different clinical and demographic variables influence perceptual differences in pain remains a poorly understood area.

Finally, how the type of painful stimulus influences pain perception and what biological and clinical implications underpin these differences are interesting lines for further research and innovation in the area of pain perception in psychosis.

In any case, learning more about the relationship between schizophrenia and pain could help us to better understand the pathways and mechanisms of this disease. Above all, it would help to know what specific limitations and needs these patients may have in case they suffer from a physical illness that causes pain and how to facilitate their medical care without delay and thus avoid complications that could otherwise be triggered.

Strengths and limitations

The present review is based on an exhaustive search both in the five bibliographic databases used, those with the greatest coverage in the field of biomedical literature, and in the number of terms used in the search strategy. This ensures that the results presented show the best scientific evidence published up to the time of the search. On the other hand, it facilitates the updating of the results of other reviews of a similar nature. In addition, this study has focused on experimental studies with a control group, in which a provoked stimulus has been performed. In this way, we have tried to reduce the variability and biases of other studies.

However, there are two limitations to be considered when evaluating the results. On the one hand, the heterogeneity of the studies included in the overall analysis, related to the different methodologies used in the studies and the different methods of pain assessment, which limits the consistency of the conclusions and should be interpreted with caution. On the other hand, the fact that we only included studies from 2010 onwards reflects a recent and current reality, but not entirely complete with respect to all the published literature, which may have influenced the conclusions to differ from previous reviews.

CONCLUSIONS

The current state of knowledge on pain tolerance in patients with schizophrenia compared to healthy persons presents conflicting results.

The overall result of our systematic review does not support the existence of altered pain sensitivity in people with schizophrenia, although a subgroup analysis suggests that when the painful stimulus is elicited by mechanical methods, people with schizophrenia present a hypersensitivity to pain compared to healthy controls. Although these results are novel data, further studies are required to replicate these findings.

Conflicts of interest

The authors declare that there are no conflicts of interest related to the subject of this study. This work has not received any funding.

Acknowledgments

Thanks to Dr. Anne Giersch and Dr. Aude Paquet for personally providing the requested information on the Duval and Paquet articles, respectively.

REFERENCES

1. Raja SN, Carr DB, Cohen M, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161(9):1976-1982. doi:10.1097/j.pain.0000000000001939.
2. Vidal Fuentes J. Versión actualizada de la definición de dolor de la IASP: un paso adelante o un paso atrás. Rev Soc Esp Dolor. 2020. doi:10.20986/resed.2020.3839/2020.
3. Peters ML. Emotional and Cognitive Influences on Pain Experience. Mod Trends Pharmacopsychiatry. 2015;30:138-152. doi:10.1159/000435938.
4. Davis GC, Buchsbaum MS, van Kammen DP, Bunney WE. Analgesia to pain stimuli in schizophrenics and its reversal by naltrexone. Psychiatry Research. 1979;1(1):61-69. doi:10.1016/0165-1781(79)90029-5.
5. Hall KR, Stride E. The varying response to pain in psychiatric disorders: a study in abnormal psychology. Br J Med Psychol. 1954;27(1-2):48-60. doi:10.1111/j.2044-8341.1954.tb00848.x.
6. Malmo RB, Shagass C, Smith AA. Responsiveness in chronic schizophrenia. *J Pers.* 1951;19(4):359-375. doi:10.1111/j.1467-6494.1951.tb01500.x.
7. Kraepelin E. *Dementia praecox and paraphrenia.* Chicago, IL: Chicago Medical Book Cooperation; 1916.
8. Wojakiewicz A, Januel D, Braha S, Prkachin K, Danziger N, Bouhassira D. Alteration of pain recognition in

Actas Esp Psiquiatr 2023;51(1): 29-40 | ISSN: 1578-2735

schizophrenia. Eur J Pain. 2013 Oct;17(9):1385-92. doi: 10.1002/j.1532-2149.2013.00310.x. Epub 2013 Mar 25. PMID: 23529960.
9. Virit O, Savas HA, Altindag A. Lack of pain in schizophrenia: a patient whose arm was burned and amputated. Gen Hosp Psychiatry. 2008 Jul-Aug;30(4):384-5. doi: 10.1016/j.genhosppsych.2008.01.005. PMID: 18585546.
10. Buhrich N, Hayman J. Self-inflicted enucleation of both eyes. Aust N Z J Psychiatry. 1994 Jun;28(2):337-41. doi: 10.1080/00048679409075650. PMID: 7993293.
11. Stubbs B, Thompson T, Acaster S, Vancampfort D, Gaughran F, Correll CU. Decreased pain sensitivity among people with schizophrenia: a meta-analysis of experimental pain induction studies. Pain. 2015;156(11):2121-2131. doi:10.1097/j.pain.0000000000000304.
12. Boettger MK, Grossmann D, Bär K-J. Increased cold and heat pain thresholds influence the thermal grill illusion in schizophrenia. Eur J Pain. 2013;17(2):200-209. doi:10.1002/j.1532-2149.2012.00188.x.
13. Minichino A, Delle Chiaie R, Cruccu G, et al. Pain-processing abnormalities in bipolar I disorder, bipolar II disorder, and schizophrenia: A novel trait marker for psychosis proneness and functional outcome? Bipolar Disord. 2016;18(7):591-601. doi:10.1111/bdi.12439.
14. La Fuente-Sandoval C de, Favila R, Gómez-Martin D, Pellicer F, Graff-Guerrero A. Functional magnetic resonance imaging response to experimental pain in drug-free patients with schizophrenia. Psychiatry Research. 2010;183(2):99-104. doi:10.1016/j.pscychresns.2010.05.003.
15. Lévesque M, Potvin S, Marchand S, et al. Pain perception in schizophrenia: evidence of a specific pain response profile. Pain Med. 2012;13(12):1571-1579. doi:10.1111/j.1526-4637.2012.01505.x.
16. Paquet A, Plansont B, Labrunie A, Malauzat D, Girard M. Past Pain Experience and Experimentally induced Pain Perception. Issues Ment Health Nurs. 2017;38(12):1013-1021. doi:10.1080/01612840.2017.1354103.
17. Girard M, Plansont B, Bonnabau H, Malauzat D. Experimental pain hypersensitivity in schizophrenic patients. Clin J Pain. 2011;27(9):790-795. doi:10.1097/AJP.0b013e31821d904c.
18. Duval CZ, Goumon Y, Kemmel V, et al. Neurophysiological responses to unpleasant stimuli (acute electrical stimulations and emotional pictures) are increased in patients with schizophrenia. Sci Rep. 2016;6:22542. doi:10.1038/srep22542.
19. Urban-Kowalczyk M, Pigońska J, Śmigielski J. Pain perception in schizophrenia: influence of neuropeptides, cognitive disorders, and negative symptoms. Neuropsychiatr Dis Treat. 2015;11:2023-2031. doi:10.2147/NDT.S87666.
20. Guieu R, Samuélian JC, Coulouvrat H. Objective evaluation of pain perception in patients with schizophrenia. Br J Psychiatry. 1994;164(2):253-255. doi:10.1192/bjp.164.2.253.
21. Autié A, Montreuil M, Moulier V, Braha S, Wojakiewicz A, Januel D. Douleur et schizophrénie: mythe et réalité [Pain and schizophrenia: myth and reality]. Encephale. 2009 Sep;35(4):297-303. French. doi: 10.1016/j.encep.2008.04.005. Epub 2008 Oct 23. PMID: 19748365.
22. Potvin S, Marchand S. Hypoalgesia in schizophrenia is independent of antipsychotic drugs: a systematic quantitative review of experimental studies. Pain. 2008;138(1):70-78. doi:10.1016/j.pain.2007.11.007.
23. Engels G, Francke AL, van Meijel B, et al. Clinical pain in schizophrenia: a systematic review. J Pain. 2014;15(5):457-467. doi:10.1016/j.jpain.2013.11.005.
24. Stubbs B, Mitchell AJ, De Hert M, Correll CU, Soundy A, Stroobants M, Vancampfort D. The prevalence and moderators of clinical pain in people with schizophrenia: a systematic review and large scale meta-analysis. Schizophr Res. 2014 Dec;160(1-3):1-8. doi: 10.1016/j.schres.2014.10.017. Epub 2014 Nov 11. PMID: 25458569.
25. Paquet A, Plansont B, Girard M. Painful Life Events in Psychiatric Disorders: A Quantitative and Qualitative Analysis. Issues Ment Health Nurs. 2019;40(9):781-789. doi:10.1080/01612840.2019.1591546.
26. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10.1136/bmj.n71.
27. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5-TR. Fifth edition, text revision. Washington DC: American Psychiatric Association Publishing; 2022.
28. Ministerio de Sanidad. eCIE10ES; 2022 [cited 2022 Jul 19]. Disponible en: URL: https://eciemaps.mscbs.gob.es/ecieMaps/browser/metabuscador.html.
29. Lo CK-L, Mertz D, Loeb M. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. BMC Med Res Methodol. 2014;14:45. doi:10.1186/1471-2288-14-45.
30. La Fuente-Sandoval C de, Favila R, Gómez-Martín D, León-Ortiz P, Graff-Guerrero A. Neural response to experimental heat pain in stable patients with schizophrenia. J Psychiatr Res. 2012;46(1):128-134. doi:10.1016/j.jpsychires.2011.09.008.
31. Zhou L, Bi Y, Liang M, et al. A modality-specific dysfunction of pain processing in schizophrenia. Hum Brain Mapp. 2020;41(7):1738-1753. doi:10.1002/hbm.24906.
32. Vaughan S, Failla MD, Poole HM, et al. Pain Processing in Psychiatric Conditions: A Systematic Review. Review of General Psychology. 2019;23(3):336-358. doi:10.1177/1089268019842771.
33. Sakson-Obada O. Pain perception in people diagnosed with schizophrenia: where we are and where we are going. Psychosis. 2017;9(4):358-366. doi:10.1080/17522439.2017.1344294.
34. Antioch I, Ciobica A, Paulet M, Bild V, Lefter R, Timofte D. Pain manifestations in schizophrenia - clinical and experimental aspects in human patients and animal models. Psychiatr Danub. 2015;27(2):142-152.

SUPPLEMENTARY MATERIAL

Supplementary Material 1	Estrategias de búsqueda

PUBMED

1	(Pain[Title/Abstract] OR "hypersensitive to pain"[Title/Abstract] OR "hyposensitivity to pain"[Title/Abstract] OR "insensitivity to pain"[Title/Abstract] OR "Pain assessment"[Title/Abstract] OR "Pain experience"[Title/Abstract] OR "Pain Hypersensitivity"[Title/Abstract] OR "pain hyposensitivity"[Title/Abstract] OR "Pain insensitivity"[Title/Abstract] OR "Pain intensity"[Title/Abstract] OR "Pain perception"[Title/Abstract] OR "Pain reactivity"[Title/Abstract] OR "pain sensitivity"[Title/Abstract] OR "Pain threshold*"[Title/Abstract] OR "Pain tolerance"[Title/Abstract] OR Hyperalgesia[Title/Abstract] OR Hypoalgesia[Title/Abstract] OR Nociception[Title/Abstract])
2	schiz*[Title/Abstract]
3	#1 AND #2
4	(Pain OR Hyperalgesia OR "Pain Perception" OR "Pain Threshold" OR Nociception OR "Pain Measurement"[MeSH Terms])
5	(Schizophrenia[MeSH Terms])
6	#4 AND #5
7	#3 OR #6

EMBASE Elsevier

1	(pain:ab,ti OR 'hypersensitive to pain':ab,ti OR 'hyposensitivity to pain':ab,ti OR 'insensitivity to pain':ab,ti OR 'pain assessment':ab,ti OR 'pain experience':ab,ti OR 'pain hypersensitivity':ab,ti OR 'pain hyposensitivity':ab,ti OR 'pain insensitivity':ab,ti OR 'pain intensity':ab,ti OR 'pain perception':ab,ti OR 'pain reactivity':ab,ti OR 'pain sensitivity':ab,ti OR 'pain threshold*':ab,ti OR 'pain tolerance':ab,ti OR hyperalgesia:ab,ti OR hypoalgesia:ab,ti OR Nociception:ab,ti)
2	schiz*:ab,ti
3	#1 AND #2
4	'schizophrenia'/exp
5	'pain'/exp OR 'hyperalgesia'/exp OR 'hypoalgesia'/exp OR 'nociception'/exp OR 'pain threshold'/exp OR 'pain measurement'/exp
6	#4 AND #5
7	#3 OR #7

Actas Esp Psiquiatr 2023;51(1): 29-40 | ISSN: 1578-2735

Supplementary Material 1 continuation | Estrategias de búsqueda

PsycINFO (Ebscohost)

1	mainsubject(schizophrenia OR schiz*)
2	mainsubject("Pain" OR "Somatosensory Disorders" OR "Pain Perception" OR "Pain Measurement" OR "Pain Thresholds")
3	#1 AND #2
4	(ti(Pain OR "hypersensitive to pain" OR "hyposensitivity to pain" OR "insensitivity to pain" OR "Pain assessment" OR "Pain experience" OR "Pain Hypersensitivity" OR "pain hyposensitivity" OR "Pain insensitivity" OR "Pain intensity" OR "Pain perception" OR "Pain reactivity" OR "pain sensitivity" OR "Pain threshold*" OR "Pain tolerance" OR Hyperalgesia OR Hypoalgesia OR Nociception) OR ab(Pain OR "hypersensitive to pain" OR "hyposensitivity to pain" OR "insensitivity to pain" OR "Pain assessment" OR "Pain experience" OR "Pain Hypersensitivity" OR "pain hyposensitivity" OR "Pain insensitivity" OR "Pain intensity" OR "Pain perception" OR "Pain reactivity" OR "pain sensitivity" OR "Pain threshold*" OR "Pain tolerance" OR Hyperalgesia OR Hypoalgesia OR Nociception))
5	(ti(schizophrenia OR schiz*) OR ab(schizophrenia OR schiz*))
6	#4 AND #5
7	#3 OR #6

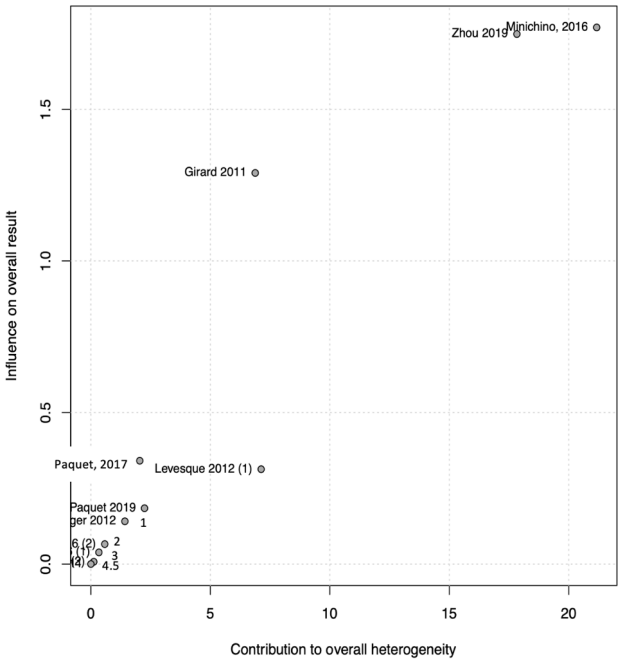
WOS (SSCI Y SCI)

1	TS=(Pain OR "hypersensitive to pain" OR "hyposensitivity to pain" OR "insensitivity to pain" OR "Pain assessment" OR "Pain experience" OR "Pain Hypersensitivity" OR "pain hyposensitivity" OR "Pain insensitivity" OR "Pain intensity" OR "Pain perception" OR "Pain reactivity" OR "pain sensitivity" OR "Pain threshold*" OR "Pain tolerance" OR Hyperalgesia OR Hypoalgesia OR Nociception)
2	TS=(schiz*)
3	#1 AND #2

SCOPUS

1	TITLE-ABS-KEY (pain OR "hypersensitive to pain" OR "hyposensitivity to pain" OR "insensitivity to pain" OR "Pain assessment" OR "Pain experience" OR "Pain Hypersensitivity" OR "pain hyposensitivity" OR "Pain insensitivity" OR "Pain intensity") OR TITLE-ABS-KEY ("Pain perception" OR "Pain reactivity" OR "pain sensitivity" OR "Pain threshold*" OR "Pain tolerance" OR hyperalgesia OR hypoalgesia OR Nociception)
2	TITLE-ABS-KEY (schiz*)
3	#1 AND #2

Supplementary Material 2 | Scatter plot



Scatter Plot. Se han numerado las citas de los nombres que no se leen bien y se escriben a continuación:

1- Boettger, 2012

2- Duval, 2016 (2)

3- Duval, 2016 (1)

4- Levesque, 2012 (2)

5- De la Fuente-Sandoval, 2011

Supplementary Material 3 | Escala de Newcastle-Ottawa (NOS)

ESTUDIOS	**Minichino, 2016**	**Duval, 2016**	**Paquet 2017**	**Paquet 2019**	**Zhou 2019**	**Levesque 2012**	**De la Fuente Sandoval 2011**	**Girard 2011**	**Boetteger 2012**
SELECCCIÓN									
Definición de caso	*	*	*	*	*	*	*	*	*
Representatividad de los casos	-	-	-	-	-	-	-	-	-
Selección de controles	-	-	*	*	-	-	-	*	*
Definición de control	-	-	*	*	*	*	*	*	*
COMPARABILIDAD	*	*	*	*	*	*	*	*	*
EXPOSICION									
Evaluación de la exposición	-	-	-	-	-	-	-	-	-
Mismo método de verificación de casos y controles	*	*	*	*	*	*	*	*	*
Tasa de no-respuesta	*	*	*	*	*	*	*	*	*
	4	4	6	6	5	5	5	6	6

Actas Esp Psiquiatr 2023;51(1): 29-40 | ISSN: 1578-2735