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Clinical Pain in Schizophrenia: A Systematic Review

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ABSTRACT

The number of studies about clinical pain in schizophrenia is sparse. Conclusions on pain sensitivity in people with schizophrenia are primarily based on experimental pain studies. This review attempts to assess *clinical* pain, that is, everyday pain without experimental manipulation, in people with schizophrenia. PubMed, PsycINFO, Embase.com, and Cochrane were searched with terms related to *schizophrenia* and *pain*. Methodological quality was assessed with the Mixed Methods Appraisal Tool. Fourteen studies were included. Persons with schizophrenia appear to have a diminished prevalence of pain, as well as a lower intensity of pain when compared to persons with other psychiatric diseases. When compared to healthy controls, both prevalence and intensity of pain appear to be diminished for persons with schizophrenia. However, it was found that this effect only applies to pain with an apparent medical cause, such as headache after lumbar puncture. For less severe situations, prevalence as well as intensity of pain appears to be comparable between people with schizophrenia and controls. Possible underlying mechanisms are discussed. Knowledge on pain in schizophrenia is important for adequate pain treatment in clinical practice.

Perspective: This review presents a valuable insight into clinical pain in people with schizophrenia.

Schizophrenia is a severe mental disorder with an estimated incidence of 15 per 100,000 persons.³⁷ The nature of the disorder is heterogeneous, making it difficult to treat as well as investigate. Schizophrenia is mainly characterized by symptoms such as hallucinations, delusions, cognitive impairments, and avolition.² A symptom that has received relatively little attention is the experience of pain. Various anecdotal case studies have described how clinical pain (ie, naturally occurring pain without experimental provocation) in, for example, appendicitis, fractures, and abdominal surgical emergencies seems reduced in persons with schizophrenia. A possible explanation for this finding might be a reduced sensitivity to pain in schizophrenia.^{6, 20, 21, 40, 41 and 44} When considering the neuropathology of schizophrenia, which is prominent in prefrontal and medial temporal areas,²⁵ a decline in the experience of pain is plausible. This possible insensitivity to pain has been addressed in several experimental studies in persons with schizophrenia. Thermal,^{13, 14 and 16} electrical,^{8 and 11} cold,³ reflex,²⁴ and tactile stimulation^{22 and 28} have been utilized to assess pain threshold and pain tolerance in schizophrenia. A considerable part, but not all, of these experimental pain studies concluded that persons with schizophrenia appear to be less sensitive to pain compared to healthy controls.^{3, 8 and 13} An alternative explanation might be that people with schizophrenia *express* pain to a lesser extent instead of *experiencing* a reduction in pain.⁹ When investigating pain, the difference between the aspects of pain should be taken into account. Pain can be divided into the sensory-discriminative aspect, mainly representing the intensity and location of pain; the motivational-affective aspect, representing the affective component of pain; and the cognitive-evaluative aspect, which integrates cognitive processes such as memory.³⁸ The neural pathways processing these aspects might be differently affected in schizophrenia, resulting in different outcomes depending on which aspect of pain is mainly evaluated.

Results from experimental studies, which mainly test acute pain, should be considered with caution. Abilities required to judge experimental pain, such as a rapid response to express pain or evaluating feelings of pain, might be altered in schizophrenia.²² Indeed, when pain was tested with manipulations more similar to a standard medical examination, for example, a *hypersensitivity* to pain emerged in persons with schizophrenia.²² Pain reaction might also differ according to type of experimental manipulation (eg, electrical or ischemic pain stimulation), as appears to be the case, for example, in major depressive disorder.⁵ Clinical pain is the type of pain for which people seek medical help.⁴⁵ Several studies suggest a differential response to clinical pain compared to experimentally induced pain.^{17, 19 and 32} Thus, if clinical pain differs from experimentally induced pain,^{17 and 32} outcomes from experimental pain studies in schizophrenia might not be completely representative for clinical pain in daily life. Consequently, it seems too coarse to conclude that people with schizophrenia are less sensitive to pain in general, when only experimental pain is assessed. Taking clinical pain into account will therefore provide a more complete insight into possible alterations in pain experience in people with schizophrenia. Therefore, the goal of the present review is to address studies in which clinical pain experience in people with schizophrenia was examined.

METHODS

Search strategies and inclusion criteria were documented in a protocol in advance. To identify articles regarding pain perception in schizophrenia, PubMed, PsycINFO, Embase.com, and Cochrane were searched until May 2013. The search strategy was based on title and abstract, MeSH terms, and thesaurus terms for *schizophrenia* and *pain*, *pain perception*, *pain management* or *pain measurement*. The search strategy used in PubMed can be found in Supplementary Appendix I. Specific search strategies performed in other literature databases are available on request. Additionally, reference lists of relevant publications on schizophrenia and pain were reviewed for eligible studies.

Publications were eligible for inclusion when the study assessed clinical pain experience in human adults with schizophrenia. Clinical pain is understood to mean every type of pain that has not been experimentally manipulated (eg, thermal or electrical stimulation). In order to provide a complete overview, all types of clinical pain were assessed (eg, pain after surgical interventions, pain in daily life, or chronic pain). Data analyses should be of a quantitative nature, not qualitative, meaning that analyses were performed on quantitative data. Only subjects with schizophrenia (ie, not schizoaffective disorder or psychosis) were eligible for inclusion in order to specify the target population.

The following languages were considered for inclusion: English, German, Dutch, and Portuguese. Publications were assessed for inclusion or exclusion in 2 steps. The first selection was based on screening titles and abstracts of retrieved publications. This process was independently performed by 2 researchers (J.G.D. and G.E.). Then, full texts of remaining publications were screened. Disagreement about inclusion or exclusion of a study was resolved by consensus. Data extraction for included studies was performed independently by 2 researchers (G.E. and A.L.F./B.v.M./E.J.A.S.). A flowchart of the inclusion process can be found in Supplementary Appendix II.

The Mixed Methods Appraisal Tool (MMAT) was used as an instrument to assess methodological quality of included studies.⁴² Total rating scores are descriptive of quality of the study and may vary from 0 to 100%. The ratings on the MMAT are included in Table 1 and are added in the text as * for 25%, ** for 50%, *** for 75%, and **** for 100%. Higher percentages indicate better methodological quality. This was determined by 4 criteria: presence of selection bias in the sample, validity of measurements, correction for cofounders in the analysis, and integrity of outcome data. Criteria were assessed by dichotomous answer possibility, with each “yes” adding another 25% to the score. MMAT assessment was performed independently by 2 researchers (G.E. and A.L.F./B.v.M.). Disagreement on the score of the MMAT was resolved by discussion.

[TABLE 1.]

RESULTS

A total of 14 studies met our inclusion criteria. All studies, their characteristics, and relevant findings are listed in Table 1. MMAT results show that 2 studies scored 25% on methodological criteria,^{18,48*} 4 studies scored 50%,^{4,15,26,50**} 6 studies scored 75%,^{10,12,30,31,46,49***} and 2 studies met all criteria for methodological quality.^{1,7****}

Prevalence of Pain

Persons With Schizophrenia Compared to Those With Other Psychiatric Disorders

In comparison with people with other psychiatric disorders—for example, endogenous depression, neurotic/mixed depression, or anxiety neuroses (see Table 1 for details regarding diagnoses)—the percentage of people with schizophrenia indicating no pain was the highest.^{15**} Of note is that this study did not mention the type of pain. Similarly, compared to persons suffering from other psychiatric disorders such as hysteria (24%) and depressive neuroses (45%), the percentage of people with schizophrenia having chronic pain appeared to be lower (2%).^{10***} In this study, only subjects with “mania (affective psychosis)” or “drug dependence” as a diagnosis had a lower prevalence of chronic pain than people with schizophrenia. The authors identified chronic pain as pain with a duration of at least 6 months. In both studies, the type of pain was not further specified. When pain was examined regardless of duration, 37.2% of a group of people with schizophrenia had pain complaints.^{50**} When the affected part of the body was examined in this group, the head was the most reported site of pain (39.4%), and pain lasted longer than 6 months for more than half of the participants. Although no statistical comparisons were made between the studied group with schizophrenia and other psychiatric disorders, the authors confirmed a lower prevalence of pain complaints in people with schizophrenia than in people with other types of psychiatric illnesses.^{50**}

In only 1 study with different psychiatric populations, a specific type of pain, that is, menstrual pain—in particular headache—was examined.^{12***} Again, the percentage of women with schizophrenia who did not suffer from a headache (56.4%) was higher than women with neurosis (41.7%), but somewhat lower than those with affective disorders (60.0%). Unfortunately, data analyses did not focus on the comparison between the psychiatric populations but on each psychiatric group in comparison to a control group (see next section).

In sum, these 4 studies suggest that pain is less prevalent in people with schizophrenia when compared to people with other psychiatric diseases.

People With Schizophrenia Compared to Controls

Compared to the general population, people with schizophrenia showed the same prevalence of chronic pain, indicated as pain lasting longer than 6 months.^{1****} The most frequent locations of pain were the abdomen, head and face region, and lower part of the spinal cord. In line with this finding, in participants with and without schizophrenia, both the absence of headache (56.4% and 56.1%, respectively^{12****}) and the presence of headache (48.1% and 41%, respectively^{31****}) was similar, and irrespective of its type, for example, migraine.^{31****} However, a *lower* prevalence of certain types of pain (eg, arthritis) has been found in veterans with schizophrenia when compared to controls without schizophrenia. In that study, a *higher* prevalence of other types of pain (eg, headache) has been observed.^{7****} Headache after a lumbar puncture occurred much less in patients with schizophrenia, compared to controls,^{4**} for example, 6% and 31%, respectively,^{48*} and 4.7% and 25%, respectively.^{18*} A lower prevalence of pain has also been observed in people with schizophrenia who were suffering from a heart condition.^{26**} In that study, myocardial infarction and coronary occlusion without pain occurred in 60% of people with schizophrenia, compared to a general population in which the prevalence of a painless presentation of these heart conditions was much lower (range 0–61%).

Taken together, it appears that prevalence of pain resulting from an apparent medical cause (eg, lumbar puncture or myocardial infarction) is lower in people with schizophrenia compared to controls. For pain without an apparent medical cause, the studies suggest that prevalence of pain is comparable to controls.

Intensity of Pain

People With Schizophrenia Compared to Those With Other Psychiatric Disorders

A survey (n = 1,072,477) among nursing home residents suffering from various psychiatric disorders demonstrates that people with obsessive-compulsive disorder showed the highest pain intensity and people with schizophrenia and bipolar disease the lowest.^{49****} According to the authors, a possible explanation is pain apathy, caused by alterations in mood and sensory processing. When intensity and pain characteristics in a group of persons with schizophrenia were addressed, 25% of the participants had severe pain intensity, 50% had moderate pain intensity, and 25% had mild pain intensity.^{50**} For subjects participating in these 2 studies, no apparent medical cause for their pain was noted. When pain after a lumbar puncture was examined, severity of headaches was lower in subjects with schizophrenia than in subjects with affective disorders.^{4**}

In sum, the findings suggest that people with schizophrenia compared to other psychiatric disorders may experience a lower intensity of pain, irrespective of the cause.

People With Schizophrenia Compared to Controls

Pain was assessed at 2 and 5 hours after an operation in persons with schizophrenia and controls.^{30***} The findings showed that at both moments of measurement, pain intensity, as assessed by a visual analog scale, was significantly lower in persons with schizophrenia than the control group. The lower pain intensity was also reflected in a lower use of the analgesic pentazocine.^{30***} In the 1 person with schizophrenia experiencing headache after lumbar puncture, no analgesic treatment was required. In contrast, pain relief was necessary for almost all subjects from the control group who suffered from severe post-lumbar puncture headache.^{18*}

In contrast to the above-mentioned findings, when headache in schizophrenia was investigated regardless of etiology, this type of pain was of equal intensity in persons with and without schizophrenia.^{31***} Another study found that the score on the subscale Bodily Pain of the Medical Outcomes Study 36-Item Short Form, assessing pain intensity, was one of the best predictors for being a person with schizophrenia, instead of being a person belonging to the control group.^{46***} It must be noted that this score did not significantly differ per group in this study.

In summary, it appears that the intensity of pain is lower in people with schizophrenia compared to healthy controls in situations that involve an apparent medical cause. No difference appears to exist between subjects with schizophrenia and controls for pain (eg, headache) without such a cause.

DISCUSSION

Prevalence of Pain

Our findings suggest that people with schizophrenia have a lower prevalence of pain compared to people with other psychiatric disorders. Although none of the studies included people with somatoform disorders, where pain is an actual symptom of the disorder, it should be noted that 1 study did report on psychogenic pain in people with schizophrenia compared to controls. In that study, prevalence of pain was higher.^{7****} When compared to controls, pain appears to be less prevalent in people with schizophrenia when it regards apparent medical conditions (eg, myocardial infarction, lumbar puncture). This difference was not found for pain without such an apparent cause.

Intensity of Pain

When compared to people with a psychiatric disorder, people with schizophrenia appear to have a lower intensity of pain. When people with schizophrenia were compared with control subjects without a psychiatric disorder, intensity of pain was lower for people with schizophrenia when it concerned situations in which pain was the result of an apparent medical cause. Again, when the pain was not related to a medical situation (eg, lumbar puncture), a difference appeared to be absent.

A Possible Explanation for a Decrease of Pain in Persons With Schizophrenia

A possible explanation for the finding of a decrease in pain in people with schizophrenia emerges from the study of Kuritzky and colleagues.^{31***} They observed that a large percentage of people with schizophrenia (40%) who indicated that they had a pain complaint had never before reported this complaint. According to these authors, people refrain from complaining about pain in order to avoid being a burden and to avoid hospitalization.^{31***} We argue that particularly these reasons might explain why people with schizophrenia might also complain less of pain in case of, for example, an operation, lumbar puncture, or myocardial infarction.

The question arises whether a decrease in complaining about pain also means that persons with schizophrenia *experience* less pain. A decrease in pain experience might be due to the deviant processing of the motivational-affective aspect of pain.³⁴ It has been suggested that the processing of motivational-affective aspects of pain requires an intact neuronal circuit connecting the limbic system and the frontal lobe.³⁵ A decline in the processing of the motivational-affective pain aspects might therefore be due to a dysfunction of the frontal lobe in schizophrenia.^{18*} It is known that the frontal lobe, in particular the prefrontal cortex, plays a role in processing motivational-affective aspects of pain.³⁵

Indeed, from all persons with schizophrenia who complained of headache, not everybody said to *experience* pain as well (84.6%).^{31***} We argue that this might be due to a deviant processing of the motivational-affective aspects of pain. This difference between experiencing pain (or pain perception) and pain behavior (or pain expression) is clinically relevant: A person might experience pain but not necessarily behave accordingly.³⁴

Next to a neuropathological point of view, as described above, firm conclusions about people with schizophrenia being less sensitive or reactive to pain as an explanation for reduced pain experience in schizophrenia cannot be drawn—either from a physiological point of view (for example, an increased pain threshold and tolerance)²⁴ or from a biochemical point of view (for example, high activity of central endorphins).⁹ Bonnot and coworkers stipulate that an increased response to pain such as atypical pain has also been observed in persons with schizophrenia. It has been suggested that people with schizophrenia may show an alteration in pain experience because of a decline in among others cognitive functions.^{9 and 27}

A final explanation for a reduced pain experience in persons with schizophrenia might be the use of antipsychotics. Antipsychotics have been shown to have analgesic efficacy.⁴⁷ However, in a meta-analysis investigating experimental pain in schizophrenia, this analgesic effect was found *not* to explain the observed diminished pain response in persons with schizophrenia.⁴³ In one of the included studies, postoperative scores on a visual analog scale also appeared not to be influenced by antipsychotics.^{30***} Antipsychotic medication might also be beneficial for cognition,²⁹ subsequently influencing pain, although the positive effect of antipsychotics on cognition has not consistently been found.²³

Limitations and Suggestions for Future Studies

Several limitations should be taken into account. First, it must be noted that schizophrenia is a complex psychopathological disorder, with heterogeneity in symptoms: Two persons may display a completely different set of symptoms and yet both be diagnosed with schizophrenia. Negative symptoms of schizophrenia, such as avolition and affective flattening, have been put forward as a reason for refraining from complaints about pain to, for example, a physician,^{7****,16} although people are indeed capable of precise description of pain.^{31***} Whether persons display mostly negative or positive symptoms might already partly determine pain outcomes. Second, conclusions about an alteration in pain experience in schizophrenia in the present study might be weakened by the fact that criteria for the diagnosis of schizophrenia have changed over time, and a number of studies were conducted decades ago. Third, our MMAT quality assessment indicates that not every included study was of optimal methodological quality, which might bias our conclusions. Fourth, the method of pain assessment might partly determine the outcome of the studies. For example, presence of pain (sensory-discriminative aspect) might be different from experience of pain (motivational-affective aspect), as mentioned before.^{31***} Therefore, future studies should not only assess presence of pain, but also inquire about intensity and other aspects of pain, as well as type of pain (eg, chronic or acute pain).^{7****,12***,30****,31***}

In order to achieve a comprehensive assessment of pain, instruments should be chosen carefully. For example, the McGill Pain Questionnaire is developed to inquire about sensory-discriminative as well as motivational-affective and cognitive-evaluative aspects of pain.³⁹ Not only should the aspect of pain guide the choice of the instrument, but comprehension of pain rating scales also should be taken into account. For example, understanding facial expressions that represent pain is found to be impaired in schizophrenia.³⁶ This makes use of the Faces Pain Scale less suitable for this group.

In conclusion, lack of awareness of possible alterations in pain in schizophrenia might result in an undertreatment of pain, particularly concerning the motivational-affective aspect, because this aspect plays an important role in the decision to ask for medical help.⁴⁵ Together with the fact that prevalence of painful physical illnesses

(eg, hepatitis, osteoporosis, cardiovascular disease, and dental problems) is increased in schizophrenia,³³ knowledge about pain in schizophrenia is needed to treat people adequately.

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Table 1. Overview of Included Studies Assessing Clinical Pain in Schizophrenia

STUDY	MMAT SCORE	STUDY DESIGN	SUBJECT CHARACTERISTICS	DETAILS DIAGNOSIS	OUTCOME VARIABLE	METHODS	RESULTS
Delaplaine et al, 1978 ^{15**}	50%	Cross-sectional	227 subjects participated; 65 people were diagnosed with schizophrenia, other diagnoses were schizo-affective psychosis (n = 4), endogenous depression (n = 10), neurotic/mixed depression (n = 19), mania (n = 8), anxiety neurosis (n = 4), hysterical personality (3), antisocial personality (n = 7), inadequate/passive aggressive personality (n = 13), retarded (n = 5), organic brain syndrome (n = 19), no diagnosis (n = 1), other personality disorders (n = 13), transient situational disturbance (n = 28), alcoholism (n = 20), drug addiction (n = 2), or another diagnosis (n = 6).	Schizophrenia	Presence, site and severity of pain (severe, moderate, mild)	Standardized survey in psychiatric hospital about occurrence and characteristics of pain. If pain was not reported spontaneously, people were asked about it. Analyses performed were χ^2 tests.	Pain was less common in schizophrenia compared to the other psychiatric disorders under study.
Chaturvedi, 1987 ^{10***}	75%	Cross-sectional	500 consecutive psychiatric patients: schizophrenia (n = 110), affective psychosis (n = 87), anxiety states (n = 40), depressive neurosis (n = 100), hysteria (n = 37), "other neurosis" (n = 15), drug dependence (n = 27), and "others" (n = 84).	Diagnosis of schizophrenia in consultation with psychiatrist	Presence of chronic pain (ie, daily pain/pain once every 2 d, lasting longer than 6 mo)	Chronic pain was determined by patients' reports. Relatives provided additional information.	1.8% of people with schizophrenia had chronic pain, compared to an average of 18.6% of all psychiatric patients (no <i>P</i> values provided).

Table 1. Continued

<i>STUDY</i>	<i>MMAT SCORE</i>	<i>STUDY DESIGN</i>	<i>SUBJECT CHARACTERISTICS</i>	<i>DETAILS DIAGNOSIS</i>	<i>OUTCOME VARIABLE</i>	<i>METHODS</i>	<i>RESULTS</i>
Watson, 1981 ^{50**}	50%	Cross-sectional	78 subjects (46 men, mean age 30.3; 32 women, mean age 37.4) diagnosed with schizophrenia	Diagnosis was based on "appropriate changes of thought, volition and affect, and evidence at some point during the illness of the presence of first rank symptoms of Schneider in the absence of coarse organic brain disease."	A verbal description (interview) concerning pain and pain characteristics	Examination of pain characteristics (duration, location, and intensity) and descriptions	37.2% of subjects with schizophrenia had pain complaints (16.7% with appropriate organic cause). 25% showed mild pain, 50% moderate pain, 25% had severe pain. Headache was the most prevalent pain complaint.
Coppen, 1965 ^{12***}	75%	Cross-sectional	616 participants: 151 women with a psychiatric diagnosis (neurosis [n = 49], affective disorder [n = 41], or schizophrenia [n = 61], mean age 35.5 y) and a control group (n = 465). Subjects were recruited from 3 psychiatric institutions and their outpatient departments.	The diagnosis was derived from the consultant in charge.	Severity of pain and headache related to menstrual period	3 groups of women with a psychiatric disorder were compared to a matched control group on a questionnaire regarding menstrual disorders (among which pain and headache). Questions on menstrual pain and headache were answered on a 4-point scale (nil, slight, moderate, and severe).	Women with schizophrenia complained of significantly less pain when compared to their matched controls ($P < .05$).
de Almeida et al, 2010 ^{1****}	100%	Cross-sectional	205 persons with schizophrenia, mean age 37 y	Schizophrenia (diagnosed according to ICD-10 criteria)	Prevalence and quality of chronic pain, that is, pain lasting more than 3 mo	Questionnaires about prevalence and quality of chronic pain during the past week and at time of interview	36.6% of the subjects experienced chronic pain. Descriptions of pain were similar to those found in the McGill Pain Questionnaire, indicating people are capable of describing their pain.

Table 1. Continued

<i>STUDY</i>	<i>MMAT SCORE</i>	<i>STUDY DESIGN</i>	<i>SUBJECT CHARACTERISTICS</i>	<i>DETAILS DIAGNOSIS</i>	<i>OUTCOME VARIABLE</i>	<i>METHODS</i>	<i>RESULTS</i>
Kuritzky, 1999 ^{31***}	75%	Case-control	208 subjects participated: persons with schizophrenia (n = 108), at least 2 y of treatment, mean age 35.6, and a group of people without schizophrenia (n = 100)	Schizophrenia as diagnosed by DSM-III-R criteria, in a chronic stage (ie, at least 2 y of treatment); control subjects did not have a diagnosis	Type, location, frequency, severity, duration, and complaints of headache were assessed by using the questionnaire.	Questionnaire about characteristics of headache was administered. Analyses were performed with a Pearson χ^2 test.	Prevalence, type, and intensity of headache was similar for controls and patients ($P = .3$). Frequency was higher in schizophrenia ($P = .04$). A significant reduction in duration of headache after treatment was found in schizophrenia ($P = .0009$). Only 84.6% who complained of headache also claimed to experience pain.
Birgenheir et al, 2013 ^{7****}	100%	Cross-sectional	A total of 5,195,551 individuals participated. Diagnoses were schizophrenia/schizoaffective disorder (n = 93,874), bipolar disorder (n = 96,186), depressive disorder (n = 757,807), or no diagnosis (n = 4,247,684).	Schizophrenia/schizoaffective disorder (referred to as "schizophrenia") according to health care providers using ICD-9-CM	Presence of arthritis, back pain, chronic noncancer pain, migraine headache, tension and other headache, psychogenic or neuropathic pain (ICD-9-CM)	Presence of pain and psychiatric diagnosis (derived from electronic medical records)	Compared to people without schizophrenia, bipolar disorder, or depressive disorder, people with schizophrenia were more likely to have chronic pain (OR = 2.10), migraine (OR = 1.13), or other headache (OR = 1.46) and psychogenic pain conditions (OR = 2.72). Adversely, arthritis (OR = .93) and neuropathic pain (OR = .94) were less likely to occur in schizophrenia.

Table 1. Continued

STUDY	MMAT SCORE	STUDY DESIGN	SUBJECT CHARACTERISTICS	DETAILS DIAGNOSIS	OUTCOME VARIABLE	METHODS	RESULTS
Ballenger, 1979 ^{4**}	50%	Case-control study	74 persons diagnosed with schizophrenia undergoing lumbar puncture	Schizophrenia	Presence, intensity, and duration of headache after lumbar puncture	Headache was examined after lumbar puncture. Analyses were performed with χ^2 -test.	Compared to healthy controls, prevalence of headache was lower ($P < .05$) and duration was shorter ($P < .05$). Compared to people with affective illness, headaches occurred as often but with a shorter duration ($P < .01$) and less severely ($P < .05$).
Torrey, 1979 ^{48*}	25%	Case-control study	126 subjects, 100 persons who were diagnosed with schizophrenia and underwent lumbar puncture, 26 controls without schizophrenia	Schizophrenia	Presence and duration of headache after lumbar puncture	Headache was examined after lumbar puncture. No P values are provided.	Subjects with schizophrenia experienced less headaches than controls: 6% of subjects with schizophrenia and 69% control subjects had headaches.
ElMallakh, 2005 ^{18*}	25%	Case-control	41 subjects participated: 21 subjects with schizophrenia (age range 22–50 y) and 20 healthy controls	Schizophrenia	Presence and intensity of headache after lumbar puncture	Unknown, t-test was performed.	25% of controls developed headache compared to 4.7% of subjects with schizophrenia. Patients experienced headaches less frequently and less intensely ($P < .04$).
Hussar, 1965 ^{26**}	50%	Cross-sectional	123 persons with schizophrenia who experienced myocardial infarction or coronary occlusion. All subjects were male and older than age 40 y.	Chronic schizophrenia (mean duration 24 y)	Presence of painless myocardial infarction, as described in clinical report	Of 343 subjects with schizophrenia, 220 died of myocardial infarction/coronary occlusion; 123 subjects survived. The clinical reports of these 123 subjects were examined postmortem. Descriptive statistics were presented. No P values were provided.	60% of the 123 patients with schizophrenia experienced no pain in chest or surrounding areas in a myocardial infarction or coronary occlusion.

Table 1. Continued

STUDY	MMAT SCORE	STUDY DESIGN	SUBJECT CHARACTERISTICS	DETAILS DIAGNOSIS	OUTCOME VARIABLE	METHODS	RESULTS
Walid et al, 2009 ^{49***}	75%	Cross-sectional	A total of 1,072,477 residents participated; diagnoses were schizophrenia (n = 146,462), dementia (n = 283,904), depression (n = 459,269), bipolar disorder (n = 24,206), anxiety (n = 153,573), or obsessive-compulsive disorder (n = 5,063).	Schizophrenia (according to ICD-9 criteria)	Pain presence and intensity was obtained from medical records.	Use of pain parameters (presence and intensity) from national nursing home survey. Correlation coefficients were calculated.	A very small negative correlation ($r = -.048$) existed between schizophrenia and pain. The DSPI score for schizophrenia was third lowest, after bipolar disorder and dementia.
Kudoh*, 2000 ^{30***}	75%	Case-control	A total of 75 people who underwent surgery for fractures: 50 people with schizophrenia (n = 25 of these subjects with schizophrenia received antipsychotics) and 25 controls. Age ranged from 34 to 67 y for people with schizophrenia, the range for the control group was 33-65 y.	Schizophrenia, diagnosis was made by independent psychiatrists according to DSM-IV criteria.	Intensity of pain, as indicated by VAS scores	VAS scores (assessed by trained nurse) at 2 and 5 h, 1st, 2nd, and 3rd day post-surgery. ANOVA and unpaired t tests were performed.	Patients with schizophrenia reported lower VAS scores at 2 hours and 5 hours post-surgery than patients without schizophrenia ($P < .05$). VAS on postoperative days 1, 2, and 3 were similar for both groups. Analgesics consumption was lower for people with schizophrenia ($P < .05$).
Sciolla, 2003 ^{46***}	75%	Case-control	137 middle-aged and elderly people with schizophrenia (n = 102) or schizoaffective disorder (n = 35) were compared with 77 healthy controls. Mean age of the people with schizophrenia was 57.9 y (8.9), healthy controls were on average 66 y (10.6).	Diagnosis of schizophrenia (and schizoaffective disorder) based on DSM-IV criteria	Prevalence and burden of pain, as measured by the 2 items on bodily pain in the SF-36	SF-36 questionnaire was administered. Analyses were performed by using t tests and logistic regression.	Scores of patients were decreased on every summary score except "bodily pain" ($P = .37$), indicating there was no difference on pain. In a multivariate logistic regression, "bodily pain" came out as a significant predictor of group membership (Wald test z-ratio = 6.225, OR = 1.021).

Abbreviations: MMAT, Mixed Methods Appraisal Tool; ICD-10, International Classification of Diseases, 10th edition; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, third edition, revised; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; OR, odds ratio; DSPI, Disease Specific Pain Intensity Scale (with higher values indicating higher levels and rates of maximum pain per disease); DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; VAS, visual analog scale; ANOVA, analysis of variance; SF-36, Medical Outcome Study 36 item Short Form Health Survey.

NOTE. Studies are presented in the order in which they appear in the text.

*Kudoh and colleagues partly used experimental stimulation of pain; these data were not included in this table.

PubMed:

#1 Schizophrenia

"Schizophrenia and Disorders with Psychotic Features"[Mesh] OR "Schizoid Personality Disorder"[Mesh] OR "Schizotypal Personality Disorder"[Mesh] OR Schizophreni*[tiab] OR "Dementia Praecox"[tiab] OR "Dementia Praecox"[tiab]

#2 Pain

"Pain"[Mesh] OR pain*[tiab] OR ache*[tiab] OR "Pain Threshold"[Mesh] OR "Pain Measurement"[Mesh] OR "Hyperalgesia"[Mesh] OR hyperalgesi*[tiab] OR allodynia*[tiab] OR "Analgesia"[Mesh] OR analgesi*[tiab] OR "Pain Perception"[Mesh] OR "Nociception"[tiab]

#3 Filter: Adults

NOT (("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh] OR adolescen*[tiab] OR child*[tiab] OR schoolchild*[tiab] OR infant*[tiab] OR girl*[tiab] OR boy*[tiab] OR teen[tiab] OR teens[tiab] OR teenager*[tiab] OR youth*[tiab] OR pediatri*[tiab] OR paediatr*[tiab] OR puber*[tiab]) NOT ("Adult"[Mesh] OR adult*[tiab] OR man[tiab] OR men[tiab] OR woman[tiab] OR women[tiab]))

#5 Publication types filter/animals:

NOT ("addresses"[Publication Type] OR "biography"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular works"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type]) NOT (animals[mh] NOT humans[mh])

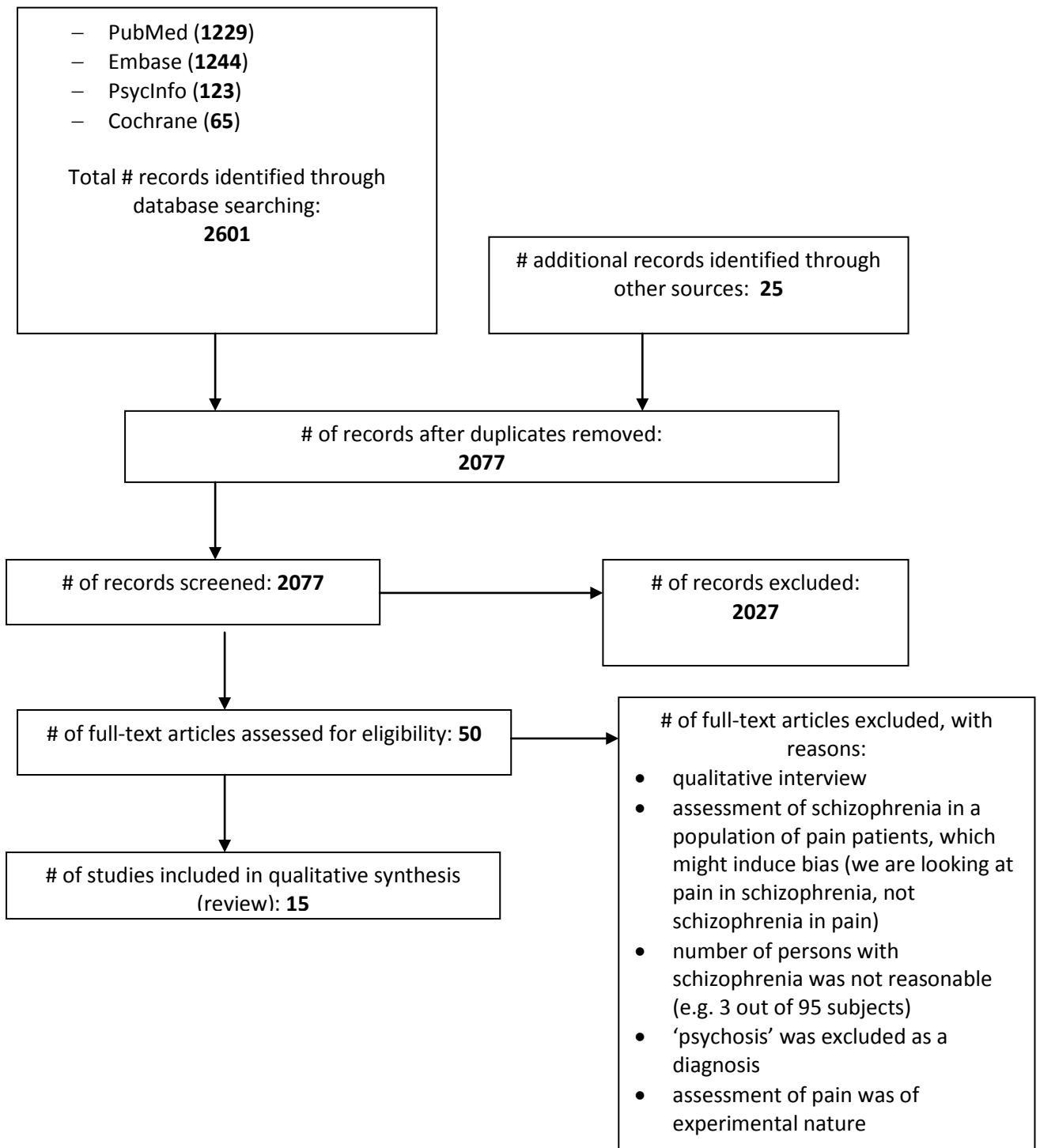
Search	PubMed	Items found
#42	Search #41 NOT (("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh] OR adolescen*[tiab] OR child*[tiab] OR schoolchild*[tiab] OR infant*[tiab] OR girl*[tiab] OR boy*[tiab] OR teen[tiab] OR teens[tiab] OR teenager*[tiab] OR youth*[tiab] OR pediatri*[tiab] OR paediatr*[tiab] OR puber*[tiab]) NOT ("Adult"[Mesh] OR adult*[tiab] OR man[tiab] OR men[tiab] OR woman[tiab] OR women[tiab]))	1222
#41	Search #40 NOT ("addresses"[Publication Type] OR "biography"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular works"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type]) NOT (animals[mh] NOT humans[mh])	1277
#40	Search #38 AND #39	1421
#39	Search "Pain"[Mesh] OR pain*[tiab] OR ache*[tiab] OR "Pain Threshold"[Mesh] OR "Pain Measurement"[Mesh] OR "Hyperalgesia"[Mesh] OR hyperalgesi*[tiab] OR allodynia*[tiab] OR "Analgesia"[Mesh] OR analgesi*[tiab] OR "Pain Perception"[Mesh] OR "Nociception"[tiab]	570869
#38	Search "Schizophrenia and Disorders with Psychotic Features"[Mesh] OR "Schizoid Personality Disorder"[Mesh] OR "Schizotypal Personality Disorder"[Mesh] OR Schizophreni*[tiab] OR "Dementia Praecox"[tiab] OR "Dementia Praecox"[tiab]	126370

Appendix 1. An example of the search and searchterms, as performed in PubMed.

Appendix II. Flowchart of the inclusion process of the systematic search.

Clinical pain in schizophrenia – Gwenda Engels

Search performed: May 2nd 2013*



*Systematic search was repeated 1 year after commencement of by GE in order to include most recently published articles. May 2nd 2013 was the most recent search.