TECHNICAL COMMENTARY

Pain sensitivity

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Introduction

Pain is defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage,” and pain is perceived as both a sensory and an emotional experience. There is an important distinction between the physiological responses to pain (nociception) and the behavioural responses or self-reported perception of pain. Pain perception is quantified using psychophysical measures, which are based on a subjective scale; and signal detection measures, which are based on discriminative thresholds and response criteria [1]. Outcomes of pain perception include pain reactivity, sensory threshold, pain threshold, and pain tolerance, as well as self-reporting of the pain experience.

A notable misperception of pain has been suggested in patients with schizophrenia, for example the presence of hypoalgesia (reduced experience of painful sensation). Absence of pain reporting in typically painful comorbid conditions can have significant consequences including the potential for misdiagnosis, as well as delays in treatment or necessary surgical intervention, which can ultimately lead to worsened morbidity and increased mortality[1, 2]. The distinction needs to be made between the physiological and behavioural responses of schizophrenia patients to painful stimuli, to understand which of these components is affected in pain misperception.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist which describes a preferred way to present a meta-analysis[3]. Reviews were assigned a low, medium or high possibility of reporting bias* depending on how many items were checked. Reviews rated as having less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if sample or effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[4]. The resulting table represents an objective summary of the available evidence, although the conclusions

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are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found four systematic reviews that met our inclusion criteria[1, 2, 5, 6].

- Moderate to high quality evidence suggests schizophrenia is associated with a significantly reduced pain response following nociceptive stimuli in several modalities, unrelated to outcome measure (including pain reactivity, sensory threshold, pain threshold and pain tolerance), modality, medication status and disease state. Physiological responses to a nociceptive stimulus were also altered.
- Moderate to high quality evidence suggests no differences in rates of *clinically relevant* pain between patients with schizophrenia and controls. Moderate quality evidence suggests the prevalence rate of clinically relevant pain in patients with schizophrenia is 34.7% and clinically relevant headache is 29.9%.
- Moderate quality evidence suggests schizophrenia is associated with reduced pain reporting in typically painful conditions.

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Bonnot O, Anderson GM, Cohen D, Willer JC, Tordjman S

Are patients with schizophrenia insensitive to pain? A reconsideration of the question

Clinical Journal of Pain 2009; 25(3): 244-252f

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Comparison 1	**Prevalence of pain reporting rates in people with schizophrenia.**
Summary of evidence	**Moderate quality evidence (large samples in clinical studies, unable to assess precision or consistency, direct) suggests schizophrenia is associated with reduced pain reporting in typically painful conditions.**
Clinical studies of pain sensitivity	
Six clinical studies, N = 435, report between 52% and 80% of included schizophrenia patients report an absence of pain in typically painful conditions, including myocardial infarction, perforation of peptic ulcer, acute appendicitis, bone fractures, and headache following lumbar puncture.	
Case reports of pain sensitivity	
Nine case reports, N = 56 schizophrenia patients report an absence of pain in typically painful conditions, including peptic ulcer, ruptured appendix, perforation of peptic ulcer, acute abdomen, perforation of small bowel, and bone fractures	
Consistency in results‡	No measure of consistency is reported.
Precision in results§	No measure of precision is reported.
Directness of results‖	Direct
Comparison 2	**Comparison of pain perception in people with schizophrenia vs. other psychiatric disorders or healthy controls.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess precision or consistency, direct) suggests schizophrenia is associated with an altered pain perception. Physiological responses were also altered.**
Pain perception	

13 studies, N = 917, investigated five measures of pain perception.

Three studies reported reduced pain reactivity in schizophrenia (based on verbal report), one study reported no significant difference to controls (based on an objective measure of pain reactivity, the nociceptive RIII reflex).

Three studies reported increased sensory threshold in schizophrenia (based on verbal report), one study reported no significant difference to controls (based on objective measure, electrodermal recovery).

Two studies reported increased pain threshold in schizophrenia, one study reported no significant difference to controls (all based on verbal report).

Two studies reported increased pain tolerance in schizophrenia, one study reported no significant difference to controls (all based on verbal report).

Two studies reported decreased pain reporting in schizophrenia, one study reported the opposite result, and one study reported no significant difference to controls (all based on verbal report).

Physiological response to pain

5 studies, N = 641

One study reported increased skin conductance level, plasma cortisol response and electromyogram response in schizophrenia following cold stress.

Four studies report on other physiological measures including a reduced pupillary response, reduced blood pressure response, reduced cerebral glucose levels and increased skin temperature following thermal stressors in schizophrenia.

Consistency in results	Results appear inconsistent.
Precision in results	No measure of precision is reported.
Directness of results	Direct

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

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Comparison	**Comparison of pain response in people with schizophrenia vs. healthy controls.**

TECHNICAL COMMENTARY

Pain sensitivity

Summary of evidence	**Moderate to high quality evidence (large samples, precise, unable to fully assess consistency, direct) suggests schizophrenia is associated with a significantly reduced pain response following nociceptive stimuli across several modalities.** **Outcome measure, modality, medication status and disease state were all shown to have no confounding effects.**
Pain response	
Significant, small to medium-sized effect of reduced pain response in patients; 12 studies, N = 583, *g* = 0.441, 95%CI 0.173 to 0.709, *p* = 0.001 *Significant, large effect of increased sensory threshold in patients;* 3 studies, N = 174, *g* = 0.883, 95%CI 0.557 to 1.208, *p* = 0.0001 *Significant, large effect of increased pain threshold in patients;* 6 studies, N = 355, *g* = 0.881, 95%CI 0.388 to 1.374, *p* = 0.0001 *Significant, small effect of increased pain response to thermal stimuli in patients;* 5 studies, N = 261, *g* = 0.384, 95%CI 0.128 to 0.640, *p* = 0.003 *Significant, medium-sized effect of increased pain response to electrical stimuli in patients;* 5 studies, N = 257, *g* = 0.682, 95%CI 0.237 to 1.128, *p* = 0.003 *Significant, medium-sized effect of reduced pain response in medication-free patients;* 5 studies, N = 224, *g* = 0.581, 95%CI 0.304 to 0.858, *p* = 0.0001 *Significant, small to medium-sized effect of reduced pain response in medicated patients;* 8 studies, N = 405, *g* = 0.465, 95%CI 0.105 to 0.825, *p* = 0.011 *Significant, small to medium-sized effect of reduced pain response in acute patients;* 7 studies, N = 329, *g* = 0.489, 95%CI 0.262 to 0.716, *p* = 0.0001 *Significant, medium-sized effect of reduced pain response in patients using validated measures;* 9 studies, N = 468, *g* = 0.587, 95%CI 0.333 to 0.841, *p* = 0.0001	
Consistency in results	No measure of consistency is reported.
Precision in results	Precise
Directness of results	Direct

Singh MK, Giles LL, Nasrallah HA

Pain insensitivity in schizophrenia: trait or state marker?

Journal of Psychiatric Practice 2006; 12(2): 90-102

View review abstract online

Comparison 1	**Prevalence of pain reporting in people with schizophrenia.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess precision or consistency, direct) suggests schizophrenia is associated with reduced pain reporting in typically painful conditions.**
Population-based studies of pain sensitivity	
Nine of ten clinical studies (N = 673) report an absence of pain in >50% of people with schizophrenia in typically painful conditions, including coronary thrombosis, myocardial infarction, acute appendicitis, peptic ulcer disease, bone fracture, and lumbar puncture. Six of nine studies (N = 1,239) showed a low prevalence (<15%) of personal or familial schizophrenia in samples of patients with chronic pain.	
Case reports of pain sensitivity	
Eleven case reports (N = 58) report an absence of pain in typically painful conditions, including peptic ulcer, ruptured appendix, peritonitis, bone fractures, acute abdomen, and perforation of small bowel.	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct measure of chronic pain prevalence in schizophrenia.
Comparison 2	**Comparison of pain perception in people with schizophrenia vs. other psychiatric disorders or healthy controls.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess precision or consistency, direct) suggests schizophrenia is associated with an altered pain perception, particularly in subjective measures of pain reactivity, sensory threshold, pain threshold and pain tolerance. Physiological responses to a nociceptive stimulus were also altered.**
Pain perception	

19 studies, N = 1,523, investigated four measures of pain perception. Five studies reported reduced pain reactivity in schizophrenia (based on verbal report). Four studies reported increased sensory threshold in schizophrenia (based on verbal report). Three studies reported increased pain threshold in schizophrenia, one study reported the opposite result, two studies reported no significant difference to controls (all based on verbal report). Three studies reported increased pain tolerance in schizophrenia, three studies reported no significant difference to controls (all based on verbal report).
7 studies reported on the physiological response to pain. Six reported altered physiological response in various measures, one reported no significant difference to controls. Reductions were observed in pupillary dilatation, blood pressure response, somatosensory evoked potential, cerebral glucose use. Increases were observed in muscle tension and heart rate. No significant difference was observed in electrodermal recovery rate.

Consistency in results	No measure of consistency is reported,
Precision in results	No measure of precision is reported,
Directness of results	Direct

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

Schizophrenia Research 2014; 160(1-3): 1-8

View review abstract online

Comparison	**Prevalence of clinically relevant pain in people with schizophrenia and vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess precision, inconsistent, direct) suggests the prevalence of clinically relevant pain in people with schizophrenia is 34.7% and clinically relevant headache is 29.9%.** **Moderate to high quality evidence (large samples, unable to**

	assess consistency, precise, direct) suggests no significant differences in rates of clinically relevant pain between people with schizophrenia and controls.
Prevalence of clinically relevant pain	
Overall prevalence of all-cause/site non-specific pain in people with schizophrenia; 14 studies, N = 242,703, pooled prevalence = 34.7%, 95%CI 23.6 to 46.6, Q = 24622, $p < 0.0001$ No relationships were found with age, gender, pain frequency, or type of pain assessment *Prevalence of headaches in patients with schizophrenia;* 3 studies N = 94,043, pooled prevalence = 29.9%, 95%CI 3 to 69%, Q = 175.0, $p < 0.0001$ *No significant differences in the prevalence of pain compared to controls;* All-cause/site non-specific clinical pain: 7 studies, N = 4,354,732, RR 0.99, 95%CI 0.83 to 1.19 Headaches: 3 studies N = 94,043, RR 1.32, 95%CI 0.85 to 2.07	
Consistency in results	Inconsistent for prevalence rates, unable to assess RRs (heterogeneity stats not reported).
Precision in results	Precise for all clinical pain comparison with controls, imprecise for headaches comparison with controls, unable to assess prevalence rates.
Directness of results	Direct

Explanation of acronyms

CI = Confidence Interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardized mean differences (see below for interpretation of effect sizes), N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), vs. = versus

Explanation of technical terms

* Bias has the potential to affect reviews of both RCTs and observational studies. Forms of bias include; reporting bias – selective reporting or results; publication bias - trials which are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small.

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† Different effect measures are reported by different reviews.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large effect[7].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[8]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives which are correctly identified (100% sensitivity = correct

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identification of all actual positives) and specificity is the proportion of negatives which are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) which is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may be considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed[8].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C, which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available so is inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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