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PAIN MANIFESTATIONS IN SCHIZOPHRENIA - CLINICAL AND EXPERIMENTAL ASPECTS IN HUMAN PATIENTS AND ANIMAL MODELS

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SUMMARY

Pain is a subjective phenomenon, not fully understood, which is manifesting abnormally in most of the disorders. Also, in the case of schizophrenia, a psychiatric disorder marked by gross distortion from reality, disturbances in thinking, feeling and behavior, pain behaves in an unpredictable manner, just like the evolution of this mental disorder.

In this way, findings on this matter are contradictory, some pleading for decreased pain perception in schizophrenia, others for increased pain sensitivity, while there are also reports stating no differences between healthy controls and schizophrenic patients. Still, it is now generally accepted that pain perception is impaired in various ways in schizophrenics. Nevertheless, pain is a very important clinical issue in this population that needs to be clarified.

Throughout this paper, we are going to review these contradictory information regarding pain manifestations in the context of schizophrenia in both human patients and animal models, emphasizing the importance of determining pain mechanism, its particularities and evolution in the context of schizophrenic disease, so that this phenomenon could be evaluated, quantified and controlled with the intention of obtaining a superior management for this disorder and to possibly raise hopes of higher life quality and expectancy in patients suffering from schizophrenia. Also, we would like to raise awareness on this matter, making psychiatrists, general practitioners, and other medical specialists more conscious of the importance of this problem, so that medical care could improve for these patients in the future.

Key words: *pain – schizophrenia - animal models - clinical pain - experimental pain*

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INTRODUCTION

Schizophrenia is a severe disabling mental condition characterised by a seriously impaired contact with the reality, various deficiencies cognitive functions and a poor prognostic.

Regarding the pain phenomenon, this is mainly presented as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey et al. 1979). Generally, two aspects of pain are presented: the sensory-discriminative one, which includes the quality, intensity, duration and location of pain, most typically originating from the body surface (Westlund & Willis 2015) and the motivational-affective one, that includes emotional reactions (related to suffering, anxiety, depression), somatic/autonomic reflexes and endocrine changes characterizing visceral pain (Westlund & Willis 2015). Also, while the pathways for sensory-discriminative and motivational-affective pain overlap to some extent, they generally have their own neural structures and pathways (Price 1999, Casey & Bushnell 2000, Westlund & Willis 2015).

Why is it important to determine the way schizophrenic patients are feeling pain? People with schizophrenia are more likely to experience a range of physical comorbidities that may induce pain. In this way, it has been reported since long ago that schizophrenic disorder is frequently associated with physical diseases (Leucht et al. 2007), for example Stubbs et al systematic review and meta-analysis demonstrated very recently that the schizophrenic patients group is highly exposed to risk of fractures reaching about 50-100% compared to people without mental illness (Stubbs et al. 2015). In addition, the fact that people may not recognise/ report pain, may contribute to health disparities/ disguise the need for medical treatment (Mitchell et al 2014). Moreover, it cannot be forgotten the great impediment and unpleasantness that the pain phenomenon produces to the individual experiencing it. Therefore, this is why understanding pain manifestation in schizophrenia is extremely important.

Additionally, it is believed that chronic pain has the potential to restrict the recovery process from the mental illnesses (Birgenheir et al. 2013), therefore knowing more about the pain perception can help us handle better its effects. Through this paper we aim to highlight previous findings regarding the study of perception, features and development of pain in schizophrenic patients and animal models of schizophrenia so that in

the future further possibilities of quick diagnostic and recording of pain phenomenon can be developed, creating suitable conditions so that an accurate administration of pain in schizophrenic disorder to be instated.

METHODS

The gathering of the reports included in this mini-review covered articles from inception until 10th March 2015, for the following key-words "pain in schizophrenia"; "pain phenomenon and schizophrenic disease"; "pain perception in schizophrenia"; "pain vs. schizophrenia". Cross references were also considered. The main scientific databases were consulted, such as Sciencedirect, Oxford Journals, Pubmed, Google Scholar. When there were encountered papers that treated clinical or experimental pain in schizophrenic patients they were selected for inclusion. Also, studies that followed pain manifestations in animal models with induced schizophrenia were of interest. Only publications in English language were considered. First of all, a screening of titles and abstracts was conducted based on the retrieved results of the search. After selection, full texts of the remaining papers were evaluated. This process was concluded by two separate researchers (I.A. and R.L.). Any kind of disagreement in the matter of including or not publications in the mini-review was resolved by common consent.

RESULTS

Quantifying pain in schizophrenia

Quantifying pain has always been a challenge, especially considering its subjectivity. Still, there are different methods of establishing pain presence in schizophrenic patients. In this way, this can be done by standard surveys in psychiatric facilities or by using various questionnaires about pain characteristics (Engels et al. 2014). What is also interesting is that a trained observer for this studies can be a nurse, like in Kudoh`s study in 2000, who used a specific scale (VAS scores) to quantify pain (Kudoh 2000, Engels et al. 2014) or untrained personal such as the patient's relatives who can notice specific behaviour that could signal the presence of pain, like in Chaturverdi`s study from 1987 (Chaturverdi 1997). Of course, the classical way is to compare results between groups, as in schizophrenic patients vs. healthy controls of the same age and sex (Engels et al. 2014), since the aspect of age and sex is important, as an increased pain experience in women and in aging population has been reported for example (AGS 2009, Stubbs et al. 2014a), although no clear evidences are suggesting that this also applies to schizophrenia.

Still, recent meta-analysis studies, such as the one conducted by Stubbs et al., reported no notable differences between sexes, concluding that both sexes require the same attention in this matter. Moreover, the same study did not indicate that pain perception is influenced by age, which suggests of course that clinical pain should be followed across the entire life span (Stubbs et al. 2014a).

However, the literature studying pain perception in schizophrenia is still quite limited. As mentioned before, many clinical investigations are pointing to less pain sensitivity in schizophrenic patients (Fishbain 1982, Bickerstaff et al. 1988, Dwokin 1994, Kudoh 2000, Blumensohn et al. 2002, Jochum et al. 2006, Singh 2006, Becker et al. 2009), since they report that schizophrenic patients are at increased risk for various underlined conditions that are not exhibiting their classical symptoms. Moreover, most of the times the patients with schizophrenia are not even aware of these conditions (Leucht et al. 2007, Mitchell et al. 2009, de Hert et al. 2011a,b, Stubbs et al. 2014a). However, despite the lack of awareness, it has been proven in a very recent meta-analysis that schizophrenic patients are more exposed to comorbidities that may induce pain such as the risk of suffering fractures. The reasons behind this fact are not fully known, but is it suspected that antipsychotics might have a contribution (Stubbs et al. 2015a), based on the theory that antipsychotics produce hyperprolactinemia which induces reduction of bone mineral density causing increased fracture risk (Hummer et al. 2005, Stubbs 2009, Takahashi et al. 2013). Furthermore, considering that breast cancer risk appears to be increased among feminine population with schizophrenia treated with antipsychotic dopamine antagonist (Wang et al. 2002), although knowing that painful situations accompany this condition, it has been noted that rates of mammography screening are decreased in women with psychiatric disorders, especially women with severe mental illnesses, suggesting that important disparities in preventive population screening occur due to defective management of mental disorders (Mitchell et al. 2014).

Another example, is given by Hussar group who reported a long time ago the presence of myocardial infarction without pain in schizophrenic patients (Hussar 1965). Moreover, the same author is mentioning that more than a half of his selected patients with myocardial infarction died from this condition, while from the ones that survived, 60% did not experience any pain at all (Hussar 1965). Similar alarming aspects have been also reported in surgical emergencies, as for example in acute appendicitis, which is known to have higher odds to let to surgical complications and even death, if is diagnosed too late (Cooke et al. 2007, Retamero & Paglia 2012). Also, as previously mentioned, another case-report involving schizophrenia disease presents a patient without any sort of pain that was diagnosed with perforated pyloric ulcers and active gastroduodenal artery bleeding (Retamero & Paglia

2012). Likewise, other papers reported that chronic pain, migraine, headaches and psychogenic pain conditions were more likely to be found in patients with schizophrenia, while on the other side arthritis and neuropathic pain are less likely to appear in the context of the schizophrenic disorder (Birgenheir et al. 2013, Engels et al. 2014).

However, there are also other researchers that reported no significant differences between controls and patients with schizophrenia in the matter of prevalence, type and intensity of headaches (Kuritzky 1999, Engels et al. 2014).

Another key point regarding headaches was marked by the Stubbs group who followed the prevalence of reported headaches among schizophrenic patients and also a comparison between the patients and control group was determined. As a result, no statistically significant differences were observed in regard to headaches encounters in neither of the studied groups (Stubbs et al. 2014a). With this in mind, in a slightly different population, bipolar disorder patients, where a previously declared association between subjective pain and migraines is a known fact (Stubbs et al. 2015a), a recent meta-analysis also investigating this subject emphasized that people with bipolar disorder experience migraine on a common basis, a higher rate being registered in persons with bipolar disorder II (Fornaro & Stubbs 2015).

Even more, Kuritzky group stated that an increased frequency of headaches in schizophrenia has been registered (Kuritzky 1999, Engels et al. 2014). On the other hand, other reports stated that headaches in schizophrenia are less frequent and less severe (Ballenger 1979, Torrey 1979, El-Mallakh 2005, Engels et al. 2014). These contradictory results could be explained by the different protocols used, especially considering that the last studies were mainly interested in the headaches resulted after several specific medical procedures, such as lumbar puncture.

Pain after medical procedures was also the subject of Kudoh`s study, but this time post-surgery pain was targeted. Thus, by using specific VAS scores, his team found that post-surgery pain was less encountered in patients with schizophrenia, as compared with controls, immediately after the intervention (2 to 5 hours). Moreover, further observation showed similar perception of pain for both groups, but overall the percentage of analgesics consumption was lower in people with schizophrenia (Kudoh 2000).

Interestingly, other groups reported that hypoalgesia phenomenon registered in drug-free schizophrenic persons can be extended to first degree relatives even if they lack other psychopathological conditions (Hooley & Delgado 2001, Jarcho et al. 2012, Stubbs et al. 2014a).

Other aspects of pain that have been performed in this area of research are related to chronic pain. As stated in a meta-analysis where chronic pain was also followed, results indicated that no statistically important difference was encountered in the case of chronic pain in schizophrenic patients compared to age and sex matched peers (Stubbs et al. 2014a).

According to a non-comparative study under the guidance of Almeida et al, only 36.6% of the selected schizophrenic patients felt chronic pain (Almeida et al 2010). In addition, the Chaturverdi`s study agrees with the fact that people with schizophrenia experience less chronic pain (Chaturverdi 1987).

Moreover, another type of clinical pain studied in the schizophrenic group was the menstrual pain. In this way, Coppen`s report concluded that there are significantly less pain complaints during menstrual cycle in schizophrenic patients, as compared to matched controls (Coppen 1965).

As already mentioned, there are also controversies in this area of research. In this way, Strassing et al. in his study involving 2400 patients, is stating that individuals with schizophrenia are expressing a higher severity of the bodily pain, in comparison with those without the disease (Strassing et al. 2003).

However, Sciolla`s report showed that the score for bodily pain indicated no significant difference between schizophrenics and healthy subjects (Sciolla 2003, Engels et al. 2014), while de la Fuente-Sandoval who tested the neural response to experimental heat pain in schizophrenic patients, came to the conclusion that pain perception in stable schizophrenics is similar to healthy controls, noticing though that the neural processing of pain does not follow a normal pattern, even when antipshychotic treatment is administrated (de la Fuente-Sandoval et al. 2012), as we will describe immediately in the section dedicated to the relevance of treatment in schizophrenia’s pain perception.

Also, another study that comes to back up somehow the aforementioned aspects, was designed to test the reactivity of insula to aversive stimuli in patients with schizophrenia and showed no significant differences between patients and a control group in regards to neural responses during anticipation of the shock, indicating basic deficit in interoceptive perception. However, the activation of the middle insula was significantly diminished in schizophrenics (Linnman et al. 2013), aspect which comes in line with previous studies that showed an increased threshold of pain perception in schizophrenic patients (Blumensohn et al. 2002, Potvin et al. 2008, de la Fuente-Sandoval et al. 2012). Moreover, the Linnman et al. findings, that no statistically significant differences can be found in the insula reactivity to aversive stimuli between healthy controls and schizophrenics is suggesting that these patients are capable of understanding pain and furthermore, according to Almeida et al., are even capable of describing their pain accordingly to McGill Pain Questionnaire (Almeida et al. 2010).

Pain in treated vs. untreated patients with schizophrenia

As mentioned before, variations between pain reactions in schizophrenia can be also recorded by comparing treated schizophrenic patients to untreated ones. First of all, we should mention that there are studies stipulating an analgesic effect of antipshychotics (Seidel et al. 2010). These aspects are confirmed also by the findings of Kuritzky`s report, which noticed for example that after treatment initiation in schizophrenia a remarkable decrease in the duration of headache was observed (Kuritzky 1999).

There are controversial data as well in this area of research, since other authors reported that on the contrary, untreated patients suffering from schizophrenia have similar threshold as healthy controls based on the nociceptive reflex. Moreover, the same group is stating the explanation for increased pain sensitivity in schizophrenia is actually a reaction of denial, rather than not feeling pain (Guieu et al. 1994).

In addition, in another study performed by Jochum et al., significantly higher thresholds of induced pain, mainly referring to warmth perception and thermal pain onset, have been registered in acute schizophrenic patients that were antipshycotic naive for 8 weeks, as compared to healthy controls. Still, when it comes to the treatment influence, it was observed that antipshycotic medication had no effect on pain perception, as studied 3 days later after treatment was started (Jochum et al. 2006).

Also, supporting this, Potvin and Marchand reported that changes in pain perception cannot be attributed to medication effects only (Potvin & Marchand 2008).

In addition, it was previously showed that patients exposed to effective antipshychotic medication for 6 weeks are experiencing a decreased blood oxygen level-dependent response in two areas normally involved in pain processing, such as the posterior cingulated cortex and brainstem and a high blood oxygen concentration-response in superior prefrontal cortex (de la Fuente-Sandoval et al. 2012).

The same research group was also interested in studying the main differences between untreated patients vs. treated patients with schizophrenia and how this is influencing the activation of various areas which are known to be implicated in pain processing, such as the superior prefrontal cortex, insula or the posterior cingulated cortex (Apkarian et al. 2005, Becerra et al. 2001, Bentley et al. 2003, Christmann et al. 2007, Niddam et al. 2002, Peyron et al. 2010), concluding that antipsychotic medication could help in normalizing pain tolerance in schizophrenic treated patients (de la Fuente-Sandoval et al. 2010).

Animal models studies

Animal models have been used for quite some time to investigate different mechanisms in various human diseases with the main purpose to find therapeutic solutions. In this way, their use is also of great significance in the study of schizophrenia and in the understanding of how this disorder is affected by pain (Franek et al. 2010).

In addition, it has to be mentioned that although the complex pathology of schizophrenia cannot be replicated completely in animals, the use of a rat model for example has the advantage of the physiological and anatomical structural similarity between humans and the rat or mouse, as well as the fact that they are easy to obtain, maintain and handle (Lefter et al. 2014).

Since some symptoms of schizophrenia are also produced by the administration of glutamate antagonists for NMDA receptors, such as ketamine and phencyclidine, which are important indicators of the essential role of the glutamatergic system functioning in schizophrenia, it has been suggested for example that the administration of ketamine in subanaesthetic doses could create a valid animal model of schizophrenia, considering the alteration of latent inhibition and especially the social interaction (Becker et al. 2003, Becker & Grecksch 2004, Becker et al. 2009). Moreover, it was showed that the administration of typical and atypical neuroleptics could result in a significant improvement of the ketamine-altered social behaviour (Becker & Grecksch 2000, Becker & Grecksch 2004).

In addition, it seems that this model can also result in increased pain tolerance (Becker et al. 2006). In this way, it was showed that the aforementioned effect on nociception was observed only in single-housed rats, as compared to group-housed ones where it was absent. Thus, the explanation for this fact was attributed to the great influence of stress and its effect in pain sensitivity (Becker et al. 2006), especially considering the increased sociability of these animals.

Also, it has been observed that the antinociceptive effect of morphine was found to be diminished in this ketamine rat model of schizophrenia, which could suggest important changes in the opioidergic systems (Davis et al. 1982, Bernstein et al. 2002, Wiegant et al. 1992, Zhang et al. 2004, Becker at al. 2009).

Other studies were also interested in studying the relevance of both typical and atypical antipsychotics on pain perception in this ketamine-induced rat model of schizophrenia, by using morphine as a positive control. Still, both neuroleptics seem to exert a non-analgesic effect. However, it was noticed that haloperidol normalized the analgesic reaction to morphine, while for risperidone a dose-dependent growth was observed in the analgesic index, after morphine administration (Becker at al. 2009).

In addition, another animal model of schizophrenia can be induced by the neonatal intracerebroventricular administration of the quinolinic acid and N-acetyl-aspartyl-glutamate. In this way, evaluating pain perception in these animals, Franek et al. demonstrated important modifications in thermal nociception, higher

pain thresholds being reported. However, no significant modifications, as compared to controls, were found in acute mechanical nociception and the formalin test (Franek et al. 2010). Also, the same author showed elevated mechanical hyperalgesia in sciatic nerve constriction rats, which is a model of neuropathic pain (Franek et al. 2010).

Furthermore, it seems that the animal models of schizophrenia are also showing signs of dysregulation when it comes to various type of pain perception and nociceptive processing, suggesting that further studies in this area of research is also needed.

DISCUSSION

As a general aspect, we can say from the beginning that the studies regarding pain perception in schizophrenic patients had very different outcomes, sometimes even contradictory ones.

In this way, most of the studies from this area of research are reporting that patients with schizophrenia have increased tolerance to pain stimuli. In fact, the increased pain threshold has been observed even since this disease was diagnosed, Kraepelin reporting no adaptative withdrawal reactions to different types of injuries such as burns or needle picks (Kraepelin & Robertson 1919, Bonnot et al. 2009, Linnman et al. 2013).

This is also sustained by individual cases, such as the remarkable one cited by Retamero and Paglia, which could show from the beginning how important the study of pain perception in schizophrenia is, since they present details about a middle aged man diagnosed with schizophrenia who did not complain of any pain even though he presented with perforated pyloric ulcer and active gastroduodenal artery bleeding (Retamero & Paglia 2012). In addition, there are also other similar cases cited in literature regarding patients with schizophrenia that suffered from acute appendicitis or perforated bowel and did not complain about any type of pain (Bickerstaff et al. 1988, Fishbain 1982, Retamero & Paglia 2012) or presented with mild, intermittent pain, but no abdominal rigidity (Rosenthal et al. 1990, Retamero & Paglia 2012). Also, other case reports are indicating lack of pain sensitivity in medical conditions such as acute myocardial infarction (Dwokin 1994, de la Fuente-Sandoval et al. 2012) or perforated appendix (Murakami et al. 2010, de la Fuente-Sandoval et al. 2012).

Still, on the other hand, there are various reports stating no significant difference between schizophrenic patients and controls in regards to pain perception. In this way, a study conducted by de la Fuente-Sandoval concluded that pain tolerance is quite similar in clinically stable schizophrenic patients, when compared to the control group (de la Fuente-Sandoval et al. 2012).

Another relevant aspect of pain perception evaluated in a detailed meta-analysis where differences were reported is site and duration of pain. Carefully comparing these parameters, some research groups found that there were no marked variations in the prevalence of site-specific pain (headaches). Also, the prevalence of all-cause clinical pain had no disparities in schizophrenic persons compared to matched age and sex controls (Stubbs et al. 2014a).

Moreover, there are also studies describing even an increased sensitivity to pain in patients with schizophrenia, which concluded that people with schizophrenia experience pain at a higher level than controls (Strassnig et al. 2003, Stubbs et al. 2014), while also testing pain sensitivity in similar medical examination conditions resulted in a clear hypersensitivity to pain in schizophrenic patients (Girard et al. 2011, Engels et al. 2014).

In this way, the aforementioned contradictory results could have several explanations, such as the fact that the abolition of pain perception in schizophrenic patients can be explained by the different changes that occur in schizophrenia development, while also refraining from complaints about pain can be put on the negative symptoms of schizophrenia, such as avolition and affective flattening (Coppen 1965, Collins & Stone 1966, Deplaine et al. 1978, Chaturverdi 1987, Dwokin et al. 1993, Blumensohn et al. 2002, Bonnot et al. 2009, de la Fuente-Sandoval et al. 2010, 2011, Birgenheir et al. 2013).

Furthermore, as mentioned before, various pain investigations should take into account the different angles of pain perception. In this way, pain is composed of a sensory-discriminative side, which points out location and/or intensity of pain and a motivational-affective side, consisting of the affective component of pain. Plus, there is also a cognitive-evaluative side, which includes cognitive aspects such as memory and superior processes related to pain manifestions (Melzack & Casey 1968). In this case, the motivational-affective aspect of pain it is said to require intact neuronal circuitry connecting the limbic system and frontal lobe (Maeoka et al. 2012), while the abolition of pain perception might be due to the deficient functioning of the frontal lobe in schizophrenia (El-Mallakh et al. 2005, Engels et al. 2014).

Also, an important reason why pain is not recognised sometimes in schizophrenic patients is represented by the well-known fact that recognition of basic emotions is modified in this disorder (Jochum 2006, Bonnot et al. 2009, Engels et al. 2014). Additionally, considering that this deficit is connected with the inability to encode facial expression at an early phase of processing (Combs & Gouvier 2004, Bediou et al. 2007, Caharel et al. 2007, Namiki et al. 2007, Turetsky et al. 2007, Fakra et al. 2008, Wynn et al. 2008, Martins et al. 2011), usual facial pain scales cannot be used on these patients to quantify the pain process, although in normal conditions facial expression of pain have been proved to be unique and totally

different from the expression of other basic emotions (Prkachin & Solomon 2008, Simon et al. 2008, Martins et al. 2011). Still, schizophrenia is known to modify several empathy domains, which are characterized by low-level facial mirroring (Varcin et al. 2010, Matins et al. 2011) and are affecting not only the recognition of emotions, but also the affective response area and the perspective communications (Derntl et al. 2009, Martins et al. 2011).

In this way, these difficulties in expressing pain might be an important explanation for the aforementioned pain sensitivity problems, rather than a truly lack of pain in schizophrenia (Birgenheir et al. 2013, Martins et al. 2011, Bonnot et al. 2009).

Also, other authors argued that people with schizophrenia refrain from complaining about pain, because they want to avoid hospitalization (Kuritzky et al. 1999, Engels et al. 2014).

Moreover, the attention deficits that are encountered in this disorder (Jochum et al. 2006, Potvin et al. 2008), together with some specific working memory deficits (Green et al. 2007, Fakra et al. 2008, Chen et al. 2009, Martins et al. 2011) are also incriminated for clinically diminished pain sensitivity in schizophrenia.

It is also important to mention that testing results must be correlated with the pain aspects that we are evaluating (Edwards et al. 2004, Lautenbacher et al. 1994, Engels et al. 2014). In this way, clinical and experimental pain must be individually defined and differentiated. Thus, while clinical pain refers to pain perception during an acute or chronic condition, the experimental pain is the one induced to determine thresholds using various tests for mechanical, thermal, electrical nociceptive or neuropathic pain. Thus, experimental pain has predefined limits in intensity and duration and it works under various other parameters, as compared to clinical pain that can reach increased thresholds and higher duration, while putting the patients through great distress (Stubbs et al. 2014a). The difference between clinical and experimental pain in schizophrenia can also be observed in Table 1, summarizing the main studies in this area of research.

Table 1. Summarizing studies regarding pain perception in patients with schizophrenia

Study	Type of study	Clinical/non-clinical pain	What was studied	Results
Coppen 1965	Comparative	Clinical pain	Severity of pain and headache related to menstrual period	Less complaints of pain from the women with schizophrenia, as compared to their matched controls
Hussar 1965	Non-comparative	Clinical pain	Clinical reports that stated presence of painless myocardial infarction	60% of the patients included in the study experienced lack of pain in chest or surrounding areas in myocardial infarction or coronary occlusion
Deplaine et al. 1978	Non-comparative	Clinical pain	Presence, location and severity of pain (severe, moderate, mild)	Pain was not found in schizophrenia that often, as compared to other psychiatric diseases included in the study
Ballenger 1979	Comparative	Clinical pain	Headache after lumbar puncture- presence, duration	Prevalence of headache was decreased and duration was shorter in comparison with healthy control subjects. Headaches appeared as often as in people with other affective disorders, but lasted less and were less severely
Torrey 1979	Comparative	Clinical pain	Headache after lumbar puncture- presence and duration	Less headaches were encountered in people with schizophrenia – 6%, as compared with the healthy control group - 69%
Watson et al. 1981	Non-comparative	Clinical pain	Pain and pain atributes through an interview (verbal description)	Headache was the main pain complaint. There was a 37.2% of pain complaints, only 16.7% with appropriate organic cause. 25%-mild pain, 50% moderate pain, 25% severe pain
Chaturverdi 1987	Non-comparative	Clinical pain	Detemining the presence of chronic pain (daily pain/pain once every 2 days, lasting longer than 6 months) from patients reports and relatives declarations	1.8% of patients with schizophrenia showed signs of chronic pain, as compared to 18.6% from all psychiatric patients
Kuritzky 1999	Comparative	Clinical pain	The complaints of headache were quantified using a questionnaire and following type, location, frequency, severity and duration	The prevalence, type and intensity of headache were found to be similar to control group. Frequency was higher in schizophrenia. An important decrease of the duration of headache was found after treatment in schizophrenia

Table 1. Continuous

Study	Type of study	Clinical/non-clinical pain	What was studied	Results
Kudoh 2000	Comparative	Clinical pain	Post-surgery intensity of pain showed by VAS scores	Lower VAS scores were encountered at 2 hours and 5 hours post-surgery in patients with schizophrenia, as compared to the control group. Similar results of VAS score in days 1,2 and 3 in both groups. Analgesics demand was lower in people with schizophrenia
Sciolla 2003	Comparative	Experimental pain	Two items on bodily pain were studied, by the usage of SF-36 questionaire, in patients with schizophrenia and healthy controls.	Results indicated no significant differences between groups with the exception of „bodily pain" which proved to be an important predictor of group membership
ElMallakh 2005	Comparative	Clinical pain	Headache after lombar puncture- presence and intensity	Headache was present in 25% of controls and just 4.7% of the patients with schizophrenia
Jochum et al. 2006	Comparative	Experimental pain	Thermal pain onset (TPO), thermal pain tolerance and experimental pain thresholds were studied by using warmth perception (WP), in medicated and unmedicated acute schizophrenic patients	Neuroleptics did not altered pain threshold. Significanttly increased pain tolerance of WP and TPO in acute schizophrenic patients was found in comparison with controls. They suggested that changes are attributes of information-processing rather than actual pain perception deficiencies
Walid et al. 2009	Non-comparative	Clinical pain	It followed pain presence and intensity in a group of patients with schizophrenia, depression, bipolar disorder, anxiety and obsessive-compulsive disorder, from the medical records	There was a small negative correlation between schizophrenia and pain. The lowest scores of the DSPI were obtained in bipolar disorder, dementia, and then in schizophrenia
Almeida et al. 2010	Non-comparative	Clinical pain	Chronic pain- prevalence and quantity	36.6% of the studied group declared chronic pain. Their descriptions were quite similar to those found in the McGill Pain Questionnaire, meaning that they have the ability to describe their own pain
De la Fuente-Sandoval et al. 2012	Comparative	Experimental pain	Blood oxygen level dependent (BOLD) changes were assessed by using 3T functional Magnetic Resonance Imaging, that appear during experimental induced pain, through painful and non-painful thermal stimuli in medicated schizophrenic patients, gender and age-matched with normal controls.	BOLD activation varied in different areas of the brain, proving abnormal central processing of pain stimuli in patients suffering from schizophrenia, even if neuroleptic treatment was followed. No significant differences between controls and schizophrenics regarding heat pain tolerance
Birgenheir et al. 2013	Comparative	Clinical pain	The existance of pain in some psychiatric disorders like schizophrenia, bipolar disorder, depressive disorder or no diagnosis, in patients suffering from arthritis, back pain, chronic noncancer pain, migraine headache, hypertension and other headache, psychogenic or neuropathic pain, as compared to controls without the psychiatric disorders.	Patients with schizophrenia are more exposed to chronic pain, migraine, other headache and psychogenic pain conditions. On the other hand, athritis and neuropathic pain were found less frequent in schizophrenia.

Considering that the psychiatrist has the closest encounter with this type of patients he should have the capacity of discerning the presence or absence of pain manifestations. Given that, a number of reviews and researches demonstrated that persons with SMI have a shorter lifespan, their mortality rate being two or three times higher compared to general population (De Hert et al. 2011a), accentuates the necessity of closer

implication of the psychiatrist in observing its patients. Moreover, in the last years mortality has risen even in countries considered to have good quality healthcare systems (Osby et al. 2000), 60% of this mortality rate being attributed to physical illness (Parks et al. 2006, Vreeland 2007). Therefore, it appears the need to diagnose pain, an important symptom of the present physical condition, continuing with the treatment of the underlined illness.

Though, a multitude of factors can be incriminated for the poor physical health of people with SMI (Lawrence & Stephen 2010), an important role is associated to individual lifestyle choices (Parks et al. 2006). Nonetheless, disparities in healthcare access, utilization and provision add-up to these poor outcomes in the physical health of persons with SMI (Osborn et al. 2003, Nasrallah et al. 2006, McIntyre et al. 2007, Roberts et al. 2007, Fagiolini & Goracci 2009, Mitchell et al. 2009, Lawrence & Stephen 2010).

Even if many healthcare professionals do not take seriously reports of physical distress in persons with severe mental illness (Stubbs et al. 2015b), all of the latest literature and also the data we presented in this current mini-review suggests they should take into account the statements of increased risk of severe comorbid diseases this group of population is exposed to (Mitchell et al. 2009, De Hert et al. 2011b, Mitchell et al. 2012, Stubbs et al. 2015b).

CONCLUSIONS

This mini-review, which was structured as a journey following pain perception in the schizophrenic disorder, confirmed once again that there is an increased variation for the nociceptive manifestations of the schizophrenic patients and animal models of schizophrenia.

All these controversies are strongly suggesting that further studies are needed in this area of research, in order to carefully determine what kind of pain manifestations are altered in schizophrenia and how the specific therapeutically approaches for this disorder are influencing nociception. However, almost all the studies we described here are arguing on one aspect, that pain perception is somehow modified in schizophrenia and could represent an important reason for the progress or regress of disorder, especially if pain is adequately treated.

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