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Factors related to the early incidence of depressive disorder in patients with a first episode of psychosis.

Factores relacionados con la incidencia temprana de trastorno depresivo en pacientes con un primer episodio de psicosis.

Autor: **Dña. Ángela Marina Alles García**

Director/es: **D. Javier Vázquez Bourgon**

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Abstract

Introduction: although depression has been thoroughly studied in chronic psychosis, we do not have a full grasp of the role of depression during a first episode of psychosis (FEP).

Objective: identifying the predisposing factors of depression in FEP and how they relate to an early onset, as well as the clinical consequences in terms of outcome, functioning and suicide.

Method: a review of the existing literature on depression in FEP was performed by an online search in Uptodate, Medline and Embase databases, in addition to the on-going clinical trials included in Clinicaltrial.gov. The articles selected were examined with the advice of a doctor specialized in the subject.

Results: the prevalence of depression during FEP is high. Prodromal and acute depression are now emerging as key factors in the development of future depression, with post-psychotic depression rarely happening on its own. While demographic factors are not associated with depression, the association between depression and other factors such as gender, substance use, duration of untreated psychosis, and the severity of positive symptoms is contradictory. Some predisposing factors that are significantly linked to depression during all stages of the illness are insight and suicide risk. Although a worse outcome and functioning are associated with post-psychotic and persistent depression, such relationship is not present in prodromal or baseline depression.

Conclusion: since the prevalence of depression during FEP is high, an early detection and management are needed in order to improve patient outcome. However, more research into this subject is required to have better knowledge of depression in FEP.

Key words: First episode psychosis, Depression, Prevalence, Suicide, Outcome

Resumen

Introducción: aunque la depresión se ha estudiado más a fondo en la psicosis crónica, el papel de la depresión durante un primer episodio de psicosis (PEP) no se comprende completamente.

Objetivo: identificar los factores predisponentes de la depresión en PEP y cómo se relacionan con un inicio temprano, así como las consecuencias clínicas en cuanto a resultados, funcionamiento y suicidio.

Método: se realizó una revisión de la literatura existente sobre la depresión en PEP mediante una búsqueda en las bases de datos de Uptodate, Medline y Embase, además de los ensayos clínicos en desarrollo incluidos en Clinicaltrial.gov. Los artículos seleccionados fueron examinados con el asesoramiento de un médico especializado en el tema.

Resultados: la prevalencia de depresión durante PEP es alta. La depresión en las fases prodrómica y aguda está emergiendo como factor clave en el desarrollo de depresión en el futuro, mientras que la depresión post-psicótica rara vez ocurre por sí sola. Si bien no se han encontrado factores demográficos asociados con la depresión, la asociación entre la depresión y otros factores como el género, el uso de sustancias, la duración de la psicosis no tratada y la gravedad de los síntomas positivos es contradictoria. Algunos factores predisponentes que están significativamente asociados con la depresión durante todas las etapas de la enfermedad son la percepción y el riesgo de suicidio. A pesar de que un peor resultado y funcionamiento están asociados con la depresión post-psicótica y persistente, tal relación no está presente en la depresión prodrómica o aguda.

Conclusión: dado que la prevalencia de depresión durante PEP es alta, se necesita una detección y manejo tempranos para mejorar el resultado del paciente. Sin embargo, se requiere más investigación sobre este tema para tener un mejor conocimiento de la depresión en PEP.

Palabras Clave: Primer episodio de Psicosis, Depresión, Prevalencia, Suicidio, Consecuencias

1. Introduction

The term First Episode of Psychosis (FEP) refers to individuals with the initial symptoms of a psychotic illness who have not been previously treated, though they might have earlier presented prodromal symptoms or subtle premorbid signs. Within the different cases of FEP, the most common diagnosis is schizophrenia and the usual age range in which the first episode occurs is between 15 and 30 years old (Jones, 2013; McGrath et al., 2004).

In the pathogenesis of FEP, neurodevelopmental abnormalities, brain changes such as the decrease of grey matter in multiple brain regions, and epigenetic factors come together to bring about the onset of the illness (Pantelis et al., 2003; Weinberger, 1996).

The clinical manifestations of the illness include psychotic symptoms (hallucinations, delusions, thought disorganization, agitation, and aggression), neurocognitive impairment (memory, attention, processing speed and executive function), metabolic abnormalities, functional impairment and suicide (J. Addington et al., 2012; Hor & Taylor, 2010; Spelman, Walsh, Sharifi, Collins, & Thakore, 2007). Another possible form of presentation of FEP is the manifestation of depressive symptoms such as anhedonia, dysphoria, amotivation, which is usually associated with a poorer outcome of the illness (Brunett et al., 2009).

Symptoms of depression have consistently been reported frequent in patients with schizophrenia (Cotton et al., 2011; Oosthuizen et al., 2002). Due to the differences between studies, lifetime prevalence results range from 6 to 75 percent, with an estimated modal prevalence of 25 percent (S. G. Siris, 2000). Compared to the 12 percent estimated lifetime prevalence of unipolar major depression and persistent depressive disorder in adults (Hausmann & Fleischhacker, 2002), depression in psychosis entails a high prevalence rate.

As defined by the ICD 10 (World Health Organization, n.d.), post schizophrenia depression consists on a depressive episode which occurs within the illness outcomes, with positive or, usually, negative symptoms being present, though not dominant. Whether the depression is reactive or intrinsic to the illness or has been uncovered after symptom resolution is irrelevant when establishing a diagnosis. Therefore, post psychotic depression would be diagnosed if the patient meets schizophrenia criteria in the last 12 months, some symptoms are still present, depressive symptoms meet the criteria for a depressive episode, and the episode has lasted 2 weeks minimum.

For a long time, post psychotic depression or depression between episodes have been the focal points of studies about depression in psychosis. However, this definition about depression in psychosis does not include symptoms during a first episode of psychosis or at a prodromal phase and the impact of this is yet to be fully understood. This could be partly explained by the sometimes-present difficulties when diagnosing depression in psychosis, since depressive symptoms can be misinterpreted as side effects, negative symptoms, or other disorders.

Nowadays, studies focusing on FEP have used different scales in order to identify depression at this stage of the illness. Some studies (Bornheimer, 2018; Brunett et al., 2009; Lopez-Morinigo et al., 2018; Lyngstad et al., 2018; Romm et al., 2010; Upthegrove, Ross, Brunet, McCollum, & Jones, 2014) use the Calgary Depression Scale for Schizophrenia (CDSS) to differentiate between patients with and without depression during the acute phase or at follow-up (Appendix I). This interview separates depression from negative and extrapyramidal symptoms and the cut-off point is stablished at 7, with a higher score predicting moderate to severe depression(Addington, Donald; Addington, Jean; Maticka-Tyndale, 1993). To determine if depression was present in the prodromal phase, that is, a depressive episode in the previous 6 months prior to onset, the tool used was the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) (Brunett et al., 2009; Upthegrove et al., 2014). Others (R. J. Drake et al., 2004; Gardsjord et al., 2018; Lopez-Morinigo et al., 2018; Oosthuizen et al., 2002; Simonsen et al., 2018), used the depression item (G6) on the Positive and Negative Symptom Scale for Schizophrenia (PANSS) or (Cotton et al., 2011) the depression score of the Clinical Global Impressions-Severity of the Illness Scales-Bipolar Illness (CGI-BP) or the item on the Hamilton Depression Rating Scale (HAMD-17) (Dai et al., 2018; Koreen AR, 1993).

The aftermath of depression in schizophrenia can be daunting, considering it has been associated with a higher suicide risk, poor response to treatment, increased number and duration of hospitalization, cognitive and social disability, in addition to adverse life events (Buckley, Miller, Lehrer, & Castle, 2009; Conley, Ascher-Svanum, Zhu, Faries, & Kinon, 2007).

It is a known fact that psychiatric disorders are strong predictors of suicide, where the severity of the illness is related to the risk, and psychotic illnesses could not be less. Early stages such as the first episode of psychosis constitutes a very high-risk period of suicide. (Brunett et al., 2009; Tidemalm, Långström, Lichtenstein, & Runeson, 2008). When studying the suicide risk in patients with depression alone, there is a correlation between previous history and feelings of worthlessness, as well as concurrent personality disorder (Haukka, Suominen, Partonen, & Lönnqvist, 2008).

The aim of this review is to determine if there is a high prevalence of depression in patients with a first episode of psychosis (FEP), the possible predisposing factors and how this could affect the course of the illness in terms of suicide risk, cognitive outcome, answer to treatment and quality of life.

2. Methods

In order to review the current literature on depression in a first episode of psychosis and its predisposing factors, an online search was carried out on UpToDate information, scientific journals from the Medline database, via Pubmed and Embase, as well as the clinical trials included in the Clinicaltrials.gov site. The search terms “First Episode Psychosis”, “depression”, “incidence”, “prevalence”, “First Episode Schizophrenia” and “suicide” were used.

The full articles were read by the author in pursuance of selecting those suitable for our review. The studies focusing on chronic schizophrenia were initially ruled out, choosing the ones concerning a first episode of psychosis with emphasis on their depression measurement relevance. The selected articles were later examined with the advice of a doctor specialized in the subject. Given the limited research on depression in FEP, the review was completed with information extracted from previous research about depression in schizophrenia, as a means to set a knowledge base for the research, without obscuring our results regarding FEP.

Within the 29 clinical trials about First Episode Psychosis found, the 8 trials that included both the study of a first episode and measurements of depression were chosen, in addition to the ones focusing only on treatment.

Finally, with the aims of expanding the existing knowledge on the subject and answering the hypotheses raised on the relationship between depression and FEP, all the information extracted was reviewed.

3. Results

Within the scope of knowledge, depression is common during early phases of psychosis (Cotton et al., 2011; Koreen AR, 1993; Oosthuizen et al., 2002; Romm et al., 2010; S. G. Siris, 2000), whether it is in the prodromal, acute, or post psychotic phase. Similarly to depression in long-term schizophrenia, the prevalence rate of depression in FEP varies between studies, ranging from 17% to 83% (D. Addington, Addington, & Patten, 1998; Koreen AR, 1993; Romm et al., 2010). A few examples of this are the study by (Romm et al., 2010) who found a 48% rate of depression in patients with FEP and (Brunett et al., 2009) who detected an 80 % incidence rate of depression (table 1), occurring in either one or multiple phases, with prodromal depression playing a pivotal role in future events.

Study	*Number of participants*	*Depressive symptoms measure*	*Depression prevalence rate*		
			Prodromal depresion	*Baseline depression*	*Postpsycho depression*
Koreen 1993	70	HAMD-17		75%	26%
Lyngstad 2018	125	CDSS		33%	25.4%
Cotton 2012	405	CGI-BP		26.2%	14.2%
Upthegrove2009	136	SCAN/CDSS	51%	59%	39%
Bornheimer 2018	404	CDSS		12.46%	
Oosthuizen 2002	80	PANSS		56%	
Upthegrove2014	92	SCAN/CDSS	56%	59%	27%
Romm2010	122	CDSS	17%	30%	22%
Dai2017	240	HAMD-17		54.6%	

Table 1: **Prevalence rates of depression at different illness stage.** Abbreviations: HAMD-17, Hamilton Depression Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; CGI-BP, Clinical Global Impression Scale for Bipolar Disorder; SCAN, Schedule for clinical assessment in Psychiatry; PANSS, Positive and Negative Syndrome Scale.

Previous studies about depression in psychosis were focused on the emergence of symptoms after the acute episode was resolved, since it was considered the time in which depression occurred. However, this was due to the less-noticeable nature of depressive symptoms, being camouflaged when they happened during an acute episode and disappearing as the episode remitted. As a matter of fact, (Cotton et al., 2011) found a co-morbid clinical diagnosis of major depression disorder in only 29.2% of FEP patients studied with depressive symptoms.

Prodromal depression

Depressive symptoms such as altered energy levels, feelings of hopelessness, loss of interest, social isolation, concentration, appetite and sleep disturbances, are common during the prodromal phase of psychosis, being present in 28 to 76% of patients. This can last days or weeks with psychotic symptoms increasing until becoming predominant. In the study by (Brunett et al., 2009) the incidence rate of depression during this phase was 51%, while (Romm et al., 2010) reported an 17% rate in a smaller cohort.

As mentioned before, it has been suggested that prodromal depression is an essential factor for developing depression later in the course of the psychotic illness. Symptoms of depression were, in fact, more severe if the patient had suffered from depression during the prodromal phase (Brunett et al., 2009).

Acute depression

Nonetheless, prodromal depression was not the only factor when considering the development of future depression. Upthegrove et al. (2009) found that the presence of depression during the acute phase was significantly correlated to a more severe, harsher depression at follow-up, disagreeing with previous studies who failed to find an association between prodromal and post-psychotic depression, along with outcome and relapse (Koreen AR, 1993). In this study, the CDSS depression score at baseline was significantly lower in affective psychosis compared to those with non-affective psychosis (Brunett et al., 2009).

Therefore, they found that both prodromal and acute depression were predictors of future depression. This goes against previous beliefs of a depression prediction based on the extent of the positive or negative symptoms or the categorization of the illness as affective. In many cases, depression is manifested before the emergence of other symptoms, thus supporting the hypothesis of depression as a part of the illness and not as a consequence, as previously believed (Brunett et al., 2009; Oosthuizen et al., 2002).

Post-psychotic depression

With all this, depression has now been acknowledged as a main trademark of the acute episode of psychosis and happens uncommonly after a first episode is resolved (Brunett et al., 2009; Koreen AR, 1993). A higher rate of depression has been found when focusing on depression that occurs after the acute phase of FEP or near, compared to the one present when the illness is settled, being associated with different psychological phenomena (R. J. Drake et al., 2004; Upthegrove et al., 2014).

In order to understand the different mechanisms that lead to post psychotic depression, psychological models have been suggested, such as the one from Birchwood et al. in which the emergence of depression is related to an increased insight as well as the illness perception (Birchwood, M., Iqbal, Z. & Upthegrove, 2005). These models suggested that the resolution or improvement of psychotic symptoms would lead to greater insight, lowering the patient's self-esteem, and predisposing them to the development of depression (R. J. Drake et al., 2004).

In the study by Upthegrove et al. (2014), post psychotic depression was defined as a follow-up depressive episode with a Calgary Depression Scale for Schizophrenia higher than 7. A bigger sense of loss, shame, and less control were indeed related to depression, implying a higher risk, as well as low level continuing positive symptoms and a greater need for treatment. Contrary to what was initially assumed and in favour of

ICD-10's diagnosis of post-psychotic depression, insight in this study was not higher in patients with PPD.

When prodromal or acute depression are not present, the so-called post psychotic depression is uncommon to appear. Although the incidence of depression during a later stage of the illness might be high, this is related to the presence of previous symptoms of depression in a patient (Brunett et al., 2009).

3.1. Predisposing factors

One could think that the presence of depressive symptoms could be influenced by demographic factors such as education, ethnicity, or age, though previous studies (Oosthuizen et al., 2002; Romm et al., 2010; Upthegrove et al., 2014) found no significant differences in patients with and without depression in FEP.

Given the tendency of mood disorders to occur in female patients, a question arises as to whether the symptoms of depression in FEP are more frequent in women. Oosthuizen et al. (2002) found that depressive symptoms at baseline were slightly higher in women, while Romm et al. (2010) noticed an association between depressive symptoms and alcohol use in men, and excitative symptoms as well as duration of untreated psychosis (DUP) in women. In this study, 30% of women had one or more major depressive episodes (MDE) in comparison with 10-15% of men. However, in the study by Dai et al. (2018), depressive symptoms were slightly lower in women (48.1%) than men (62.2%). Finally, Upthegrove et al. (2014) found no gender differences between patients with depression and those without it.

Multiple factors could be responsible for the presence of depressive symptoms in FEP, including a subjective reaction to the illness, accompanying adverse life events, substance abuse, co-morbid major depressive disorder, anxiety disorders, or neuroleptic induced dysphoria (Oosthuizen et al., 2002). These factors could act as stressors initiating the depression or even depressive symptoms themselves could be the ones decompensating vulnerable individuals and triggering psychosis, as explained by the stress-diathesis model. Based on this model, patient vulnerability would not only be defined by specific predisposing factors, but constitute a continuum varying from high vulnerability patients waiting for psychosis to happen to the very low risk majority of people, passing through a group of population for whom stressors would be the determining factors when establishing the development of the disorder (S. G. Siris, 2000).

Premorbid adjustment with characteristics of indecisiveness and rumination might be of importance when identifying those who could benefit from a prompt assessment. Romm et al. (2010) found an association between poorer premorbid childhood social and academic functioning and level of depression at start of treatment. These individuals would therefore be vulnerable to depression, which could serve as an identifier of possible future psychosis and an early intervention target (Brunett et al., 2009). However, this vulnerability could be just a small part of a bigger picture, with

neurobiological and cognitive factors coming together to form the physiopathology of depression in FEP (Brunett et al., 2009).

Perhaps underlying a common psychopathology behind them or a susceptibility in these patients, depressive symptoms were found related to family history of psychiatric disorders, past history of major depressive disorder, suicide attempts, and higher insight (Cotton et al., 2011).

Substance use

Compared to the general population, there is a high rate (up to 50%) of substance use disorders including cannabis, stimulants, and opioids, in patients with FEP (Brunette et al., 2018). These consumptions and specifically the use of cannabis constitutes a risk factor for the development of psychosis (Moore et al., 2007). However, recent studies show no association between depression during the acute phase and the use of substances (Brunett et al., 2009), which were actually less consumed by depressed patients. Furthermore, depressed patients were less likely to be hospitalized, contradicting previous data and not explained by psychopathology differences (Cotton et al., 2011).

Duration of untreated psychosis and symptomatology

The duration of untreated psychosis (DUP) is another controversial predisposing factor of depression. While some studies found an association between a longer DUP and the severity of depressive symptoms in women (Romm et al., 2010) and suicidal ideation (Bornheimer, 2018), others failed to find this relationship (Oosthuizen et al., 2002). Whereas Brunett et al. (2009) and Upthegrove et al. (2014) only found DUP related to depression when talking about a later phase of the illness.

In this line of thought, Brunett et al. (2009) described that depression severity was not correlated with psychotic symptomatology, as a higher rate of either positive or negative symptoms did not imply a more severe depression, contrary to the results obtained by Koreen AR (1993), who found an association between depression and a greater severity of psychotic symptoms. PANSS scale score was not higher in patients with depression, a disparate finding with that obtained in the study by Dai et al. (2018), who found a higher PANSS score in those with depressive symptoms. Contrary to its relevance in post psychotic depression and suicidal ideation, the severity of positive symptoms, along with the duration of untreated psychosis, is not a strong predictor of acute depression (Bornheimer, 2018; Upthegrove et al., 2014).

However, in the study by Oosthuizen et al. (2002), baseline depression was associated with negative symptoms, though only explaining a small portion of them, while later depression was associated with both positive and negative symptoms. Therefore, depressed patients have a milder course in terms of negative symptoms. Positive symptoms, on the other hand, were not linked to depression scores, which reinforces the hypothesis of both phenomena appearing independently.

Insight

Another important factor we should consider when talking about depression in FEP is insight. Although the existing evidence of the relationship between insight and depression is divergent, this review aims to shed some light on how they affect one another.

Along with factors such as family history of depression, lack of social support, multiple hospitalizations, or recent hospital discharge, insight has been considered one of the main risk factors of depression in schizophrenia.

In order to evaluate insight in psychosis, multiple approaches can be taken. One of them is the proven reliable Insight Scale (IS), which consists of eight questions that measure awareness of illness, symptoms and need for treatment. When the result of this scale is high, this implies a greater insight (Birchwood et al., 1994). Another essentially similar measuring scale is the Schedule for Assessment of Insight scale-expanded version (SAI-E), which follows this multidimensional model of insight (Lopez-Morinigo et al., 2018). Another way of assessing insight by some studies is the insight item on the PANSS scale.

As previously explained, it was assumed that the resolution of psychotic symptoms would lead to an increased insight with a better understanding of the illness and the predisposition for the development of depression, though this was later rejected (R. J. Drake et al., 2004).

In the study by Drake et al. (2004), insight was not related to paranoia, since confounders were present in the relation between greater symptom severity and lower insight. As they hypothesised, insight was associated with depression, with better insight predicting greater depression in psychosis, especially in acute stages of the illness. In support of this, Cotton et al. (2011), found that patients with greater depression were the ones with greater insight not only at entry, but at discharge This correlation between depression and insight was also found on the study by Morinigo et al. (2018).

However, Gardsjord et al. (2018), found that better insight was linked to higher depression at baseline as well, though not at follow-up. This might be because the association is in part moderated by the severity of the illness, as recent studies have explained (Belvederi Murri M, Amore M, Calcagno P, Respino M, Marozzi V, 2016).

Moreover, in the study by Upthegrove et al.(2014), insight throughout the illness was not linked to depression. Although moderate insight was found in the number of patients studied, there were no differences in the score obtained by depressed and non-depressed patients. When breaking down the different components of the evaluation of insight, awareness of the illness and negative appraisals were higher in patients with depression in the acute phase, as well as feelings of loss, shame and entrapment. In fact, in the study by drake et al. (2004), both insight and depression were weakly related to low self-esteem, though their relation was not specified, and other factors were involved.

In spite of not being related to insight, paranoia was in fact associated with depression, as a probable cause and a strong predictor at follow-up. Although these factors were clearly related, these associations were milder as the time passed, suggesting an adjustment process. Since paranoia was not related to insight, there would be no place for treating paranoia in order to achieve greater insight, though there might be a beneficial impact on insight not dependent of paranoia. Nonetheless, treatment of positive symptoms can be the key to treating depression, specially at the acute phase when it is most important (R. J. Drake et al., 2004).

Despite the relation between insight and depression, insight has been found relevant in psychosis, predicting better outcomes.

Finally, insight has also been related to suicide risk in first-episode-psychosis (Cotton et al., 2011), though when studied further, confounders such as depression and previous suicide history were identified as the main factors increasing the association perceived. This revealed the influence previous self-harm history had on insight levels at onset (Lopez-Morinigo et al., 2018).

3.2. Clinical consequences of depression in FEP

With these results, the model of depression in FEP suggested by Upthegrove et al. (2014) consists on a base of susceptibility and environmental factors resulting in depression in the prodrome, which increases, combined with illness appraisals and voice and threat perception, future risk of depression.

In the study by Upthegrove et al. (2014), depression in the acute first episode of psychosis was associated with higher engagement and malevolence and lower benevolence scores when evaluated by the Beliefs about Voices Questionnaire (BAVQ-R), which measures different characteristics from the patient's auditory hallucinations. Moreover, the Details of Threat Questionnaire (DOT) scores were higher in depressed patients with stronger persecutors and a bigger affliction caused by menaces with an inability to manage them. Based on this, it was proposed that some of the patients who experience depression do it as a result of the personal experience of the symptoms, though this was slightly statistically significant.

Moreover, there were higher Safety Behaviour Questionnaire (SBQ) scores and negative illness appraisals as measured by the Personal Beliefs about Illness Questionnaire (PBIQ-R). Although it has been indicated that prodromal depression is an important predictor of depression, when controlled, other predictors emerge, such as negative illness appraisals. These, in contrast to positive symptoms, are not resolved as the episode settles, which contributes to the previously mentioned hypothesis of causality between depression and illness perception (Upthegrove et al., 2014).

Outcome

Depression in FEP is associated to a poorer outcome and relapse (Upthegrove et al., 2014). However, this might be stage dependant, with higher baseline depression scores

being a favourable prognostic indicator and predicting fewer negative symptoms later on, and persistent symptoms of depression or their later emergence predicting a poorer outcome (Oosthuizen et al., 2002). Other research supports this idea such as the study by Gjardsgord et al. (2018), who studied Subject Quality of Life (S-QoL) as an outcome measure by the Lehmen's Quality of Life Interview and its association with depression and functioning. Both factors showed a significant negative effect on S-QoL, with higher depressive symptoms resulting in a lower quality of life. However, this was only during the follow-up period, with baseline symptoms showing no such association. In view of this, it could be presumed that there is a different pathological base for depression at different illness stages.

Apart from the known correlation between negative symptoms and a poor outcome, in the study by Oosthuizen et al. (2002), no association between baseline depressive symptoms and outcome was found. Therefore, a higher baseline depression did not equal a worse outcome, but it implied a favourable prognostic indicator.

Different outcome measures were also analysed by Simonsen et al. (2018), who studied self-rated disability as measured by the Assessment Schedule 2.0. They found that self-rated disability was closely related to life satisfaction and depressive symptoms, as previously reported by Chudleigh et al. (2011), who also found an association with social anxiety. Although the direction between depression and self-rated disability was not clarified when evaluated at 1-year follow-up, they found baseline levels of depression to be a predictor of self-rated disability, especially in two social domains: "getting along with people" and "participation in society". Moreover, they concluded that self-rated disability was an outcome measure on its own, distinctive from functioning and life satisfaction, thus needing its appropriate assessment (Simonsen et al., 2018).

Functioning

Some research has failed to find significant association between depression and functioning. However, the study by Lyngstad et al. (2018) found a significant association, positive symptoms and apathy aside, between depression and the Global Assessment of Functioning Scale-Split version, functioning subscale (GAF-F) scores. This association between depression and poor functioning was especially relevant in patients with persistent depression, determined as having a CDSS score of 7 or higher both at baseline and at one-year follow-up.

Although the depression rate was higher during the acute phase, this did not translate into altered functioning at this phase. The prevalence of depression was higher when associated with persistent apathy, categorized as an Apathy Evaluation Scale (AES-C) score of 27 or higher at both baseline and follow up, which was found to have a higher prevalence. Associations between depression, apathy and poor functioning were especially noticeable with persistent symptoms, compared to those patients experiencing fluctuating symptoms, whose functioning difficulties were milder. Though initially considered additive, the impact produced by persistent depression and apathy was independent, underlying the different neurobiological mechanisms responsible, apart from the reduced motivation (Lyngstad et al., 2018).

Persistent depression has been linked to poor follow-up functioning by other studies such as Cotton et al. (2011), who found an association between persistent depression together with past history of a major depressive disorder and a poor outcome when evaluated at 18 months, as well as in the long term of 5-10 years in the study by Sönmez et al. (2016).

Suicide

Suicide risk is another important factor that comes in to play when it comes to the evolution of the illness. Psychotic illnesses have a high risk of suicide, being specifically higher around the time of the first episode and usually heralded by feelings of depression and hopelessness, which act as essential predictors (Brunett et al., 2009; Thorup et al., 2002).

This association between suicidal thinking, behaviour, and hopelessness has been recently studied in the meta-analysis carried out by Ribeiro et al (2018), where they found an association between hopelessness and an increased risk of ideation, attempted and consummated suicide.

In order to achieve suicide or self-harm, overdose was the main method used by studied patients. Other means such as hanging, cutting, walking in front of traffic, or jumping from a height were not presented in as a big of a magnitude, although they were not trivial (Brunett et al., 2009).

Acts of self-harm and suicidal thinking have been related to depression in FEP, being present not only during the early phases of the illness, but as it progresses. The studies by Bornheimer et al. (2018) and Melle et al. (2006), have found the prevalence rate of suicide to be highest in the first year after starting treatment; whereas others (Brunett et al., 2009) found that the majority of acts of self-harm happened during a phase in which the illness was not being treated. This might have been a result of the phase of the illness in which these studies have been performed, with the latter focusing on First Episode Psychosis.

This high risk period could be associated with greater insight, depressive symptoms (Cotton et al., 2011), as well as the duration of untreated psychosis (DUP), which has been consistently reported to be higher in patients with suicidal ideation (Bornheimer, 2018).

A better insight into the illness has been related to a higher risk of suicide in various meta-analysis (Challis, Nielssen, Harris, & Large, 2013; Hawton, Sutton, Haw, Sinclair, & Deeks, 2005). Although it was initially thought that insight preceded depression, which resulted in a higher suicide risk (R. E. Drake & Cotton, 1986), recent research into the matter has revealed that this relationship could even be beneficial (Barrett et al., 2015). The magnitude in which suicide risk is affected by insight could have been misinterpreted due to the confounding role of previous self-harm history and depression. This was brought to light by the recent study carried out by Lopez-Morinigo

(2018), where they found that previous suicide history before onset had an impact on insight.

Going back to our subject of study, there is a higher rate of depression at baseline in patients who report suicidal thoughts (Bornheimer, 2018; Cotton et al., 2011), being found together in up to 63% of patients (Brunett et al., 2009). In fact, some studies have reported an equidistant growth between suicidality and symptoms of depression, with a more severe depression resulting in a higher risk of suicide attempts (Gonzalez-Pinto A, Aldama A, Gonzalez C, Mosquera F, Arrasate M, 2007). Furthermore, previous acts of self-harm history have been significantly related to persistent depression (Cotton et al., 2011; Sönmez et al., 2016).

Although there was a decrease on the number of acts of self-harm attempted by participants of some studies at follow-up, there was an association between depression and acts of self-harm after the resolution of the first episode. When studying all the demographic factors and patient's characteristics, including gender, prodromal depression was the only predictive factor of importance (Brunett et al., 2009).

Suicide risk is therefore influenced by many factors, so our aim should be to investigate those we do not know and asses those we can identify. There is no doubt that if the presentation of suicide thinking is during the acute phase, these patients would need specific treatment for it. However, we should consider future risk, perhaps predicted by self-harm history, in order to reduce suicide rates and establish a better outcome for these patients, even in those without depression or suicide thoughts at baseline (Bornheimer, 2018). There could also be a higher risk of patients with an early onset of the illness, which could be lessened, as mentioned above, with an early intervention, although this is yet to be confirmed (Brunett et al., 2009; Lopez-Morinigo et al., 2018).

Since pharmacotherapy on its own, such as atypical antipsychotics, has not shown risk reduction, maybe we should be focusing on secondary prevention. This early intervention would consist on detecting and treating depression, hopelessness and psychosis at their earliest stages possible, especially in those considered more susceptible (Brunett et al., 2009). Another mainstay in this treatment could be cognitive therapies with family and patient psychoeducation, suicide risk evaluation, means of suicide reduction, control, and support of important life experiences (Bornheimer, 2018). In this line of treatment, there are programs such as Cognitive-Behavioural Suicide Prevention for Psychosis and skills training programs (Tarrier et al., 2013). Improving insight, however, should not be a main treatment goal, since its magnitude has been shown not to be related to future risk (Lopez-Morinigo et al., 2018).

Given the relationship between depression and suicide, it is safe to say patients would benefit from antidepressant medication. However, there is no established protocol as to the management of a first episode. With an early treatment, patients would benefit from suicide risk reduction as well as improving their functional outcomes. In order to achieve this, more in-depth knowledge about this matter would be beneficial (Upthegrove et al., 2014).

4. Discussion

For years, depressive symptoms have been recognized present in schizophrenia. However, it was not until recently that this relationship started to be studied in first episode of psychosis, with the latter being a new concept.

After reviewing the literature and answering our review aims, we can conclude that depression is frequent in patients with their first episode of psychosis. Whether it is a consequence of the scales used on its measurement and the variable prevalence of depression according to the stage of the illness or not, the range of depression prevalence obtained is very wide: 12.5-75% (Figure 1). Therefore, a consensus on establishing an all-around measurement criterion should be achieved in order to reach a definite, yet more representative, prevalence rate.

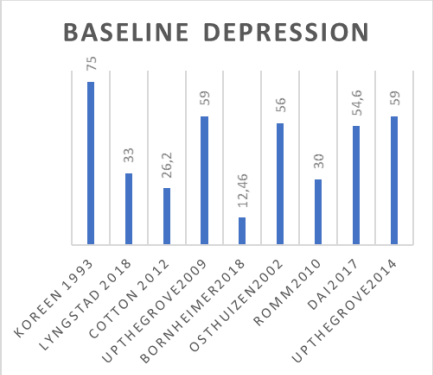

Figure 1: Baseline depression prevalences.

Unlike the preconceived idea that depressive symptoms can be confused with side effects, negative symptoms or other disorders during an acute phase of FEP where psychotic symptoms stand out, we have seen that we have enough tools to be able to identify signs of depression in these patients, thanks to the use of scales such as the CDSS (Addington, Donald; Addington, Jean; Maticka-Tyndale, 1993). We should therefore strongly consider the hypothesis of depression as a part of the illness and be aware of the importance on its assessment (Oosthuizen et al., 2002).

Apart from post psychotic depression, which has been studied more thoroughly, other important components of depression in FEP are now arising, revealing that depression can not only coincide, but precede psychosis (Romm et al., 2010). On that note, prodromal depression emerges as a main component of depression in FEP, as well as a predictor of future depression, along with the crucial role played by acute depression (Brunett et al., 2009).

Therefore, post-psychotic depression, initially considered as one of the key clinical elements in the study of FEP, and being in association with a greater insight, feelings of loss, shame, and low self-esteem (R. J. Drake et al., 2004), is now losing importance, being conceived as a consequence of these previous symptoms that act as predictors and only occasionally occurring on its own (Upthegrove et al., 2014)

The prevalence of depression varies not only with population, which could be in line with a genetic susceptibility, but also with group studies within the same population, which correlates with the evidence of no demographic association between depression and FEP (Dai et al., 2018). The information regarding gender relevance on depression in FEP is contradictory, since depressive symptoms have been found to be more severe in women in some studies (Romm et al., 2010), while others found a lower incidence in women (Dai et al., 2018), or found no differences whatsoever between genders (Upthegrove et al., 2014).

Taking into account the difficulties on measuring susceptibility (Lyngstad et al., 2018), some studies concur on the existence of patient's characteristics that make them more prone to develop depression in psychosis, such as indecisiveness, rumination, and a poorer premorbid childhood social and academic functioning (Romm et al., 2010).

Along with these characteristics, we find the knowledge about substance use as a predisposing factor of depression in these patients to be inconsistent. Another incongruous predictor of depression is the duration of untreated psychosis, though most of the literature seems to find it only associated with post-psychotic depression, just like the severity of positive symptoms (Bornheimer, 2018; Brunett et al., 2009; Upthegrove et al., 2014).

On the other hand, insight has been unequivocally proven to be significantly associated with depression during all stages of the illness (Cotton et al., 2011; R. J. Drake et al., 2004; Lopez-Morinigo et al., 2018). This relevance was mostly derived from the awareness of the illness, as well as feelings of loss, shame, and entrapment (Upthegrove et al., 2014). Paranoia was also found to be linked to depression, though of no importance in the relationship between insight and depression. What was in fact related to insight was the previous history of self-harm (Lopez-Morinigo et al., 2018).

More research into the matter is needed in order to identify the predisposing factors and shed some light into all these contradictions. The best way to achieve this might be carrying out clinical trials in patients with FEP (Appendix II). The observation and study of patients with first episode of psychosis offers great advantages when it comes to understanding the characteristics of the disease and its own psychopathology, without the interference of confounding factors such as the duration of the disease itself and the comorbidities that appear during its evolution, as well as the effects derived from treatment (Dai et al., 2018).

Understanding all these predisposing factors and the manifestation of depressive symptoms during the first episode have much to say regarding the extent of the disease. Depression in FEP was associated to worse perception of voices, stronger persecutors and distress caused by threats, together with negative illness appraisals (Upthegrove et al., 2014).

Although an unfavourable outcome has been related to depression in psychosis, it seems that baseline depression does not follow this idea. In fact, acute depression might represent a good prognostic indicator with lower negative symptoms in the future, while post-psychotic depression and negative symptoms are the ones responsible for a worse outcome, implying a lower quality of life (Gardsjord et al., 2018; Oosthuizen et al., 2002). However, one outcome domain has been associated with baseline depression, that is, self-rated disability, finding an impact on two measurements: "getting along with people" and "participation in society" (Simonsen et al., 2018).

Functioning is another clinical consequence that has been associated with depression, specifically post-psychotic. Even though depressive symptoms were higher in the acute stage, the relation between functioning and depression was only relevant in patients

with persistent symptoms. Persistent depression was thereby a predictor of poor functioning. The role of apathy was also of importance given its involvement in functioning, though independent of depression (Lyngstad et al., 2018).

Another critical factor when talking about repercussions is suicide risk, which has a high incidence during the acute phases of psychosis, with 60% of patients reporting suicidal thoughts at entry. Feelings of hopelessness during FEP can increase ideation and attempt, thus preceding suicide (Ribeiro et al., 2018). Prodromal depression was indeed the main predictor of suicide which was found, implying the need for an early assessment (Brunett et al., 2009).

Apart from depressive symptoms, a high risk for suicide has been associated with the duration of untreated psychosis, since it was during those periods that suicide rates were higher (Brunett et al., 2009). The contribution of insight in this depression-suicide tandem is uncertain, with confounding factors such as the previous history of self-harm, related in turn with persistent depression (Lopez-Morinigo et al., 2018).

Limitations

When considering all these findings, we must take into account the different limitations that could be present in each of the studies, considering the possible bias in patient selection, since patients presenting with symptoms in primary care are different from those admitted to hospitals (Dai et al., 2018); and regarding inclusion criteria, while some studies only included non-affective FES (Cotton et al., 2011) others were laxer including schizoaffective disorders (Lyngstad et al., 2018). Other variables should also be taken into account: time of follow-up, as symptoms of depression might be higher after hospital discharge or during the first time of follow-up compared to years later; treatment (although the definition of FEP includes patients without previous treatment, the treatment during the acute phase might be different between patients and we do not know the repercussions this could have on future measurements); and approaches used, with retrospective assessments presenting a higher memory bias, especially when it comes to the evaluation of prodromal symptoms.

Aside from the limitations derived from each study, this review also has some of its own, starting from the article selection process which was carried out by a single person with limited knowledge into the subject and could have been susceptible to selection bias. Moreover, not all of the existent literature about the topic could be reviewed, perhaps leaving some relevant information out of this study.

Treatment

Based on all this, we can presume that it is important to assess depressive symptoms in FEP. Therefore, a legitimate question we can ask ourselves arises: is the use of antidepressants a good therapeutic option in these cases? One could think that depressive symptoms are produced by the same mechanisms of depression in non-psychotic patients, hence benefiting from a similar therapeutic management.

The existing evidence of antidepressant therapy is derived from chronic patients, since not much research has been done regarding patients with a first episode. Clinical trials have been demonstrated successful in reducing depressive symptoms in patients with schizophrenia, with a higher efficacy once the psychotic phase diminishes (Gregory, Mallikarjun, & Upthegrove, 2017).

Moreover, depressive symptoms in a first episode of psychosis have been consistently reported to have an association with the resolution of psychotic symptoms, which leads us to believe that there might be a common psychopathological substrate causing both processes. Thus, it should be imperative to understand the nature of depression in FEP in order to establish an effective treatment (Cotton et al., 2011). One of the possible tools in reducing depression at any phase of the illness is the treatment of positive symptoms such as paranoia or delusions, given that longer duration of untreated psychosis is a predictor of depression (R. J. Drake et al., 2004).

Consequently, since most depressive symptoms are no longer present when the acute phase is over (Koreen AR, 1993; Oosthuizen et al., 2002), antidepressant therapy may be only of importance in patients with persistent depression. This would explain the efficacy found with the use of antidepressants in post-psychotic depression compared to that of an acute exacerbation (Koreen AR, 1993). As a result, treatment approaches for depression should be different according to the phase in which the patient is.

In the acute phase, antipsychotic drugs seem to be the best treatment option, though it has also been linked to a higher severity of depression, in correlation to a better insight. Although initially not perfectly fitted for patients during the acute phase, antidepressants have been used in cases of persistent symptoms which did not respond adequately to neuroleptics (Oosthuizen et al., 2002). In fact, in the study by Cotton et al. (2011), 55.6% of patients with moderate to severe depression were prescribed antidepressants, with a surprisingly higher CGI-BP score at discharge compared to patients without antidepressants.

The concomitant use of antidepressants and antipsychotics has been reported effective in reducing depression in clinical trials of patients with schizophrenia (Helfer et al., 2016), resulting in less exacerbations (Samuel G Siris, Bermanzohn, Mason, & Shuwall, 1994). However, it should be noted that there is a need for close monitoring when using both therapies simultaneously, as some antidepressants can increase antipsychotic medication levels (Upthegrove, 2009). Specifically, the use of fluvoxamine has been associated with toxic levels of clozapine (Centorrino et al., 1996).

However, antidepressants are not normally used in FEP, with the treatment of psychotic symptoms playing a crucial role during the florid episode and depressive symptoms being negligently put aside. The study by Simonsen et al. (2018), highlights the requirement of a specific assessment and treatment of depressive symptoms and social disability in early phases of first-episode psychosis, along with the treatment of psychotic symptoms. As mentioned above, most depressive symptoms disappear once the psychosis remits, so it could be argued that there is no room for improvement with

the use of antidepressants during an acute phase, with psychosocial interventions settling as a key therapy.

Persistent depression, on the other hand, has been associated with a shorter duration of treatment as well as non-compliance, which is also linked to personality disorder and persistent substance abuse (Cotton et al., 2011). This post-psychotic phase of the illness could be properly managed with the association of psychological therapies including psychoeducation and prevention of relapse, as well as assessing negative appraisals along with antidepressants if needed (Upthegrove et al., 2014).

Furthermore, there is no widespread agreement on how to manage depression in schizophrenia, let alone a first episode of psychosis (Cotton et al., 2011; Gregory et al., 2017). Apart from the above-mentioned relevance of clinical trials on establishing predisposing factors for depression in these patients, they are a key tool for comparing different treatment options, as well as observing their following repercussions. Recent clinical trials (table 2) are focusing on this matter. Thus, it would be interesting to know the results of this research in contemplation of possible future directions.

Study	NCT number	Start date	Completion date	Status	Phase	Number of participants	Interventions
Cognitive Behavioral Therapy for Patients With an Early Psychosis	NCT01511406	January 2011	October 23, 2014	Completed	2	60	Cognitive behavioral therapy
Efficacy and Safety of Quetiapine in Treating Affective Symptoms of Patients With First-episode psychosis-a Pilot Study	NCT00511277	August 2007	April 2011	Completed	4	60	Seroquel
Multifamily Psychoeducation and Cognitive Remediation for Recent-Onset Psychosis	NCT01196286	June 2010	April 2017	Completed	Not applicable	40	Multifamily Group Psychoeducation (MFG), Cognitive Remediation (CR)
Depression and Citalopram In First Episode Recovery (DECIFER)	NCT01041274	January 2010	March 26, 2018	Completed	4	95	Citalopram, Placebo Psychoeducation, Cognitive Behavioral Therapy (CBT) Functional Magnetic Resonance Imaging (fMRI)
Mediators and Moderators of Treatment Outcome in Recent-Onset Psychosis	NCT01570972	February 2010	April 2017	Completed	Not applicable	103	Group Cognitive Behavioral Therapy, Multifamily Group Psychoeducation
Biomarkers in First Episode Schizophrenia	NCT02033382	July 2012	June 2018	Active, not recruiting		40	
Oral Versus Injectable Risperidone for Treating First-Episode Schizophrenia	NCT00330551	March 2006	November 2012	Completed	4	135	Group Skills Training and Psychoeducation, Individual Case Management Oral Risperidone, Risperidone in Long-Acting Injectable Form (Consta)
Oral Risperidone Versus Injectable Paliperidone Palmitate for Treating First-Episode Schizophrenia	NCT01451736	October 2011	December 2020	Recruiting	4	170	paliperidone palmitate, risperidone

Table 2: Summary of the clinical trials about treatment in First Episode Psychosis and measurements of depression. Adapted from hhttps://clinicaltrials.gov/

Early treatment of depression in FEP would be then imperative not only for the improvement of symptoms but also as a main treatment goal to lower suicide risk, since depressive symptoms have been found associated with higher suicidality (Bornheimer, 2018; Lopez-Morinigo et al., 2018; McGinty, Sayeed Haque, & Upthegrove, 2018). As a matter of fact, one of the strategies used in the prevention of suicide is antidepressant therapy, with secondary prevention focused on hopelessness and susceptible individuals and cognitive therapies conforming possible strategies for the management of suicide and depression. Patients with previous history of self-harm would particularly benefit from this, considering hopelessness as a main risk factor (Brunett et al., 2009). Given its repercussions in functional outcome, the treatment of these symptoms would be of importance preventing a worse outcome and quality of life, constituting yet another benefit of treating depression (Gardsjord et al., 2018).

Until now, we have considered the different treatment possibilities for depression in FEP. However, as we can conclude from our review of the literature, depressive symptoms can appear even before the acute psychotic symptoms, which opens new opportunities for treatment. Can we identify susceptibility characteristics in individuals? Could any type of treatment or assessment of those vulnerable people, such as psychotherapy, offer benefits in terms of prevention or reduction of risk? These are some of the questions we should contemplate going forward, considering the positive repercussions they could have to be able to identify and treat the precursors of the illness or if the treatment of those precursors would even beneficial for it. Some people have studied high-risk groups of schizophrenia, such as Upthegrove et al. (2009), who evaluated the use of antidepressants in young people during their prodrome with successful results. Others have considered the management of these groups with the use of Cognitive-Behavioural Therapy (Morrison et al., 2004), even stating depression as the driven force of psychosis (Upthegrove, 2009).

Finally, the management of depression in FEP could be summarized in the use of antipsychotic treatment during the acute phase; antidepressants if needed, with the knowledge derived from clinical practice and yet to be further studied; and psychotherapy, along with an early assessment and active tracking of risk patients. Moreover, treatment should be individualized since mental health disorders do not always follow a strict pattern but constitute a continuum with a wide variability between individuals. Nonetheless, more research into this subject is needed in order to have a full understanding of this disorder.

5. Conclusion

In view of these results, we can conclude that there is a high prevalence of depression in people with a first episode of psychosis. Although prodromal and acute depression are related to post-psychotic depression, they seem to have different predisposing factors, which underlies the possible differences in their aetiology. The results of the on-going or already carried out clinical trials based on FEP are of vital importance to clarify these unknowns. Due to the importance depression has in FEP, patients should be correctly assessed in terms of an early detection and proper management, with the knowledge derived from clinical practice and the use of different treatment strategies, yet to be further studied. Therefore, in order to improve patient consequences in terms of functioning, outcome, and suicidality, a better knowledge of depression in FEP is required.

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Appendix I- Calgary Depression Scale for Schizophrenia (CDSS)

 Interviewer: Ask the first question as written. Use follow up probes or qualifiers at your discretion. Time frame refers to last two weeks unless stipulated. N.B. The last item, # 9, is based on observations of the entire interview.

I. **DEPRESSION: How would you describe your mood over the last two weeks? Do you keep reasonably cheerful or have you been very depressed or low spirited recently? In the last two weeks how often have you (own words) every day? All day?**

0. **Absent**
1. **Mild** - Expresses some sadness or discouragement on questioning.
2. **Moderate** - Distinct depressed mood persisting up to half the time over last 2 weeks: present daily.
3. **Severe** - Markedly depressed mood persisting daily over half the time interfering with normal motor and social functioning.

II. **HOPELESSNESS: How do you see the future for yourself? Can you see any future? Or has life seemed quite hopeless? Have you given up or does there still seem some reason for trying?**

0. **Absent**
1. **Mild** - Has at times felt hopeless over the last two weeks but still has some degree of hope for the future.
2. **Moderate** - Persistent, Moderate sense of hopelessness over last week. Can be persuaded to acknowledge possibility of things being better.
3. **Severe** - Persisting and distressing sense of hopelessness.

III. **SELF DEPRECIATION: What is your opinion of your self compared to other people? Do you feel better, not as good, or about the same as other? Do you feel inferior or even worthless?**

0. **Absent**
1. **Mild** - Some inferiority; not amounting to feeling of worthlessness.
2. **Moderate** - Subject feels worthless, but less than 50% of the time.
3. **Severe** - Subject feels worthless more than 50% of the time.
   May be challenged to acknowledge otherwise.

IV. **GUILTY IDEAS OF REFERENCE: Do you have the feeling that you are being blamed for something or even wrongly accused? What about? (Do not include justifiable blame or accusation. Exclude delusions of guilt.)**

0. **Absent**
1. **Mild -** Subject feels blamed but not accused less than 50% of the time.

2. **Moderate -** Persisting sense of being blamed, and/or occasional sense of being accused.
3. **Severe -** Persistent sense of being accused. When challenged, acknowledges that it is not so.

V. **PATHOLOGICAL GUILT: Do you tend to blame yourself for little things you may have done in the past? Do you think that you deserve to be so concerned about this?**

0. **Absent**
1. **Mild** - Subject sometimes feels over guilty about some minor peccadillo, but less than 50% of time.
2. **Moderate** - Subject usually (over 50% of time) feels guilty about past actions the significance of which he exaggerates.
3. **Severe** - Subject usually feels s/he is to blame for everything that has gone wrong, even when not his/her fault.

VI. **MORNING DEPRESSION: When you have felt depressed over the last 2 weeks have you noticed the depression being worse at any particular time of day?**

0. **Absent -** No depression.
1. **Mild -** Depression present but no diurnal variation.
2. **Moderate** - Depression spontaneously mentioned to be worse in a.m.
3. **Severe** - Depression markedly worse in a.m., with impaired functioning which improves in p.m.

VII. **EARLY WAKENING: Do you wake earlier in the morning than is normal for you? How many times a week does this happen**?

0. **Absent -** No early wakening.
1. **Mild -** Occasionally wakes (up to twice weekly) 1 hour or more before normal time to wake or alarm time.
2. **Moderate -** Often wakes early (up to 5 times weekly) 1 hour or more before normal time to wake or alarm.
3. **Severe -** Daily wakes 1 hour or more before normal time.

VIII. **SUICIDE: Have you felt that life wasn't worth living? Did you ever feel like ending it all? What did you think you might do? Did you actually try?**

0. **Absent**
1. **Mild -** Frequent thoughts of being better off dead, or occasional thoughts of suicide.
2. **Moderate -** Deliberately considered suicide with a plan, but made no attempt.
3. **Severe -** Suicidal attempt apparently designed to end in death (i.e.: accidental discovery of inefficient means).

IX. **OBSERVED DEPRESSION: Based on interviewer's observations during the entire interview. The question "Do you feel like crying?" used at appropriate points in the interview, may elicit information useful to this observation.**

0. **Absent**
1. **Mild** - Subject appears sad and mournful even during parts of the interview, involving affectively neutral discussion.
2. **Moderate** - Subject appears sad and mournful throughout the interview, with gloomy monotonous voice and is tearful or close to tears at times.
3. **Severe** - Subject chokes on distressing topics, frequently sighs deeply and cries openly, or is persistently in a state of frozen misery if examiner is sure that this is present.

Adapted from https://www.ucalgary.ca/cdss/files/cdss/english-scale-2.-2018.pdf (Calgary, n.d.)

Appendix 2-Clinical trials regarding First Episode of Psychosis and treatment

Study	NCT number	Location	Start date	Completion date	Status	Phase	Number of participants	Interventions
Efficacy and Safety of Quetiapine in Treating Affective Symptoms of Patients with First-episode psychosis-a Pilot Study	NCT00511277	Göttingen, Germany	August 2007	April 2011	Completed	4	60	Seroquel
Clinical Trial of Integrated Treatment Versus Standard Treatment in First Episode Psychosis	NCT00157313	Copenhagen, Denmark	January 1998	December 2022	Active, not recruiting	Not applicable	600	Integrated treatment, family involvement, Social skills training
Cognitive Behavioral Therapy for Patients With an Early Psychosis	NCT01511406	Oslo, Norway	January 2011	October 23, 2014	Completed	2	60	Cognitive behavioral therapy
Integrated Metacognitive Therapy in First Episode Psychosis (IMT)	NCT02131116	Indiana, United States	May 2014	December 2017	Completed	Not applicable	20	Integrated Metacognitive Therapy, Treatment as Usual
Longitudinal Long-term Study (10 Years) of the Sample of First Episode of Non-affective Psychosis: PAFIP (10PAFIP)	NCT02200588	Cantabria, Spain	September 2014	December 2019	Enrolling by invitation	Not applicable	277	
Multifamily Psychoeducation and Cognitive Remediation for Recent-Onset Psychosis	NCT01196286	Arizona, United States	June 2010	April 2017	Completed	Not applicable	40	Multifamily Group Psychoeducation (MFG), Cognitive Remediation (CR)
A Novel Treatment Approach for Self-Stigma in First Episode Psychosis (BOOST)	NCT03491852	Ontario, Canada	April 1, 2018	January 2020	Recruiting	Not applicable	40	BOOST Intervention, Waitlist Control
A Randomized Controlled Trial of Individual Therapy for First Episode Psychosis (PSTEP)	NCT00722163	Ontario, Canada	September 2007	March 2013	Unknown	1	330	Cognitive Behavioural Therapy, befriending
e-Learning & Development of an Evidence-based Psychoeducational Programme for First Episode Psychosis	NCT01783457	Barcelona/ Vizcaya/ Valencia/ Álava, Spain	January 2011	June 2015	Completed	Not applicable	177	Individual psychoeducation

Graduated Recovery Intervention Program for Enhancing Treatment for First-Episode Psychosis	NCT00307216	North Carolina, United States	April 2006	December 2008	Completed	Not applicable	46	Graduated Recovery Intervention Program (GRIP), Treatment as usual (TAU)
Comparative Study of Aripiprazole, Quetiapine and Ziprasidone in the Treatment of First Episode Nonaffective Psychosis (PAFIP2)	NCT02305823	Cantabria, Spain	October 2005	May 2014	Completed	4	203	Aripiprazole, Quetiapine, Ziprasidone
Cognitive behavioural therapy program to First-Episode Psychosis patients and cannabis abuse	NCT02319746	Alava, Spain	September 2013	September 2019	Active, not recruiting	Not applicable	100	Cognitive-behavioral therapy program to first-episode psychosis patients and cannabis abuse, Psychoeducation
Depression and Citalopram In First Episode Recovery (DECIFER)	NCT01041274	New York, United States	January 2010	March 26, 2018	Completed	4	95	Citalopram, Placebo Psychoeducation, Cognitive Behavioral Therapy (CBT) Functional Magnetic Resonance Imaging (fMRI)
Cbt for Psychosis and Affect on Psychosis Symptoms (cbtpaps)	NCT02653729		September 2015	January 2016	Completed	2	50	cognitive behaviour therapy, Espidone, Olepra, Donu
Predicting Antipsychotic Discontinuation in Psychosis (PADP)	NCT02884518	Seoul, Republic of Korea	October 4, 2016	December 2018	Active, not recruiting	Not applicable	35	PET, clinical scale
Anomalous Self-Experience in First Episode Psychosis - A Six-Year Follow-Up Study	NCT02321943	Brumunddal, Norway	February 2015	December 2016	Completed	Not applicable	56	
Effectiveness of a Mindfulness-based Group Training Addressing Social Cognition in First Episode Psychosis (AGES-Mind) (AGES-Mind)	NCT03309475	Madrid, Spain	September 1, 2018	December 31, 2020	Recruiting	Not applicable	80	SocialMIND, Psychoeducational multicomponent intervention, Psychosocial treatment,

								Psychotropic treatment
Minnesota Community-Based Cognitive Training in Early Psychosis (Mini-COTES)	NCT03079024	Minnesota, United States	May 19, 2017	May 19, 2021	Recruiting	Not applicable	150	Targeted Cognitive Training, General Cognitive Exercises
Psychoeducative Treatment of FEP With Mobile Training	NCT03161249		February 2019	January 2021	Not yet recruiting	Not applicable	50	Experimental group, Control group
Mediators and Moderators of Treatment Outcome in Recent-Onset Psychosis	NCT01570972	Arizona, United States	February 2010	April 2017	Completed	Not applicable	103	Group Cognitive Behavioral Therapy, Multifamily Group Psychoeducation
An Integrated Program for the Treatment of First Episode of Psychosis (RAISE ETP)	NCT01321177	California/ Colorado/…, United States	July 2010	July 2017	Completed	Not applicable	404	Integrated Treatment, Community Care
Biomarkers in First Episode Schizophrenia	NCT02033382	New York, United States	July 2012	June 2018	Active, not recruiting	Not applicable	40	
Multi-disciplinary Treatment for Patients Experiencing First Episode of Psychosis	NCT01216891	Maryland/New York, United States	October 2010	August 2016	Completed	Not applicable	65	Multi-element, team-oriented treatment
Optimization of Acute Treatment in First Episode Schizophrenia	NCT00157378	Munich, Germany	November 2000	December 2004	Unknown	4	300	Risperidone, Haloperidol
Omega-3 Fatty Acids Efficacy in First-episode of Schizophrenia (OFFER)	NCT02210962	Lodz, Poland	September 2011	February 2015	Unknown	4	80	essential fatty acids, olive oil
A Follow-Up Study of Schizophrenic Participants Following Treatment Discontinuation After Remission From a First Psychotic Episode	NCT00378092	Bellville, South Africa	April 2006	March 2010	Completed	4	33	Oral risperidone, Risperidone Long-Acting Injection (RLAI)
Optimizing Response in Psychosis Study (ORP)	NCT00314327	New York, United States	April 2006	November 2013	Terminated, recruitment was limited	4	1	long-acting injectable risperidone

Oral Versus Injectable Risperidone for Treating First-Episode Schizophrenia	NCT00330551	California, United States	March 2006	November 2012	Completed	4	135	Group Skills Training and Psychoeducation, Individual Case Management Oral Risperidone, Risperidone in Long-Acting Injectable Form (Consta)
A Large Pragmatic Cluster Randomized Controlled Trial of a Multi-element Psychosocial Intervention for Early Psychosis (GETUP-PIANO)	NCT01436331	Verona, Italy	April 2010	May 2012	Completed	Not applicable	626	Treatment As Usual (TAU), TAU+CBT for pts+Family Intervention+CM.
Oral Risperidone Versus Injectable Paliperidone Palmitate for Treating First-Episode Schizophrenia	NCT01451736	California, United States	October 2011	December 2020	Recruiting	4	170	paliperidone palmitate, risperidone

Adapted from https://clinicaltrials.gov/ (Medicine, n.d.)

List of Abbreviations

AES-C: Apathy Evaluation Scale
BAVQ-R: Beliefs about Voices Questionnaire
CBT: Cognitive Behavioural Therapy
CDSS: Calgary Depression Scale for Schizophrenia
CGI-BP: Clinical Global Impressions-Severity of the Illness Scales-Bipolar Illness
CR: Cognitive Remediation
DOT: Details of Threat questionnaire
DUP: Duration of untreated psychosis
FEP: First episode of psychosis
FES: First episode Schizophrenia
fMRI: Functional Magnetic Resonance Imaging
GAF-F: Global Assessment of Functioning Scale-Split version, Functioning subscale
GRIP: Graduated Recovery Intervention Progrem
HAMD: Hamilton Depression Rating Scale
ICD-10: International Statistical Classification of Diseases
IMT: Integrated Metacognitive Therapy
IS: Insight Scale
MDE: Major depressive episode
MFG: Multifamily Group Psychoeducation
ORP: Optimizing Response in Psychosis
PANSS: Positive and Negative Symptom Scale for Schizophrenia
PBIQ-R: Personal Beliefs about Illness Questionnaire
PEP: Primer episodio de psicosis
PET: Positron Emission Tomography
PPD: Post-psychotic depression
RLAI: Risperidone Long-Acting Injection
SAI-E: Schedule for Assessment of Insight Scale-Expanded version
SBQ: Safety Behaviour Questionnaire
SCAN: Schedule for Clinical Assessment in Neuropsychiatry
S-QoL: Subject Quality of Life
TAU: Treatment as usual