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DOI:
10.1093/schbul/sbw097

Document Version
Peer reviewed version

Citation for published version (Harvard):
Upthegrove, R, Marwaha, S & Birchwood, M 2017, 'Depression and schizophrenia: cause, consequence or trans-diagnostic issue?', *Schizophrenia bulletin*, vol. 43, no. 2, pp. 240-244.
https://doi.org/10.1093/schbul/sbw097

Depression and schizophrenia: cause, consequence or trans-diagnostic issue?

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Abstract word count: 87

Article word count 2638

Abstract

The presence of depression in schizophrenia has been a challenge to the Kraepelinian dichotomy, with various attempts to save the fundamental distinction including evoking and refining diagnoses such as schizoaffective disorder. But the tectonic plates are shifting. Here we put forward a summary of recent evidence regarding the prevalence, importance, possible aetiological pathways and treatment challenges that recognising depression in schizophrenia bring. Taken together we propose that depression is more than co-morbidity and that increased effective therapeutic attention to mood symptoms will be needed to improve outcomes and to support prevention.

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Prevalence of Depression in the life course of Schizophrenia

The prevalence of depressive disorder in schizophrenia has been reported to be around 40%, however the stage of illness (early vs. chronic) and state (acute or post-psychotic) factors influences figures, which can thus vary considerably[1]. In acute episodes rates are up to 60%, whilst in post-psychotic schizophrenia rates of moderate to severe depression vary between 20% in chronic schizophrenia and 50% following treatment of first episode[2]. When examining very early phases of illness, in groups identified as ultra high risk (UHR) for psychosis, high rates of 'co-morbid' axis one diagnoses are reported, with over 40% reaching criteria for a depressive disorder, outweighing anxiety or other mood symptoms[3]. When depression is investigated longitudinally in schizophrenia, the vast majority, up to 80%, of patients experience a clinically significant depressive episode at one or more time point during the early phase. This underlines how cross-sectional rates markedly underestimate the true prevalence and suggests that in the early phase of illness at least, mood symptoms may be more than 'co-morbid' experiences. The diversity in reported figures for depression is also partly attributed to the challenge in distinguishing mood symptoms from negative symptoms, suggesting a complex and as yet poorly understood overlap with other symptom dimensions at a phenomenological level[4]. Depression in schizophrenia has long been a taxonomic challenge leading to assertions that true schizophrenia is 'non-affective'; or invention of new diagnoses and broadening definitions, such as schizoaffective disorder. In DSM-V schizoaffective disorder, the occurrence of the delusions or hallucinations must be present in the absence of any serious mood symptoms for at least 2 weeks whilst the mood disorder must be present for the majority of the total duration of illness[5]. Our increasing knowledge as to the prevalence and course of depression in schizophrenia particularly, in the early years makes, the distinction between schizophrenia and new definitions of schizoaffective disorder even more challenging [2].

Importance of depression in schizophrenia

Historically there has been some thought that the presence of mood symptoms in schizophrenia may be a good prognostic indicator, with patients who have high levels of affective symptoms appearing more on the 'bipolar' rather than deficit/autistic end of a psychosis continuum model[6]. However on the contrary, evidence suggests that depression is linked to poorer outcomes in schizophrenia[2, 7]. As example, depression is the most significant factor in completed suicide in schizophrenia, more so than acting on command hallucinations[8]. Depression also has long term consequences for functional recovery and quality of life [1]. Conley et al report that those with schizophrenia and depression were significantly more likely to relapse, to be a safety concern (violent, arrested, victimized, suicidal), have greater substance-related problems and report poorer life satisfaction, mental functioning, family relationships, and medication adherence[1]. In UHR samples, reporting of psychotic like experiences in the presence of moderate depression also raises risk for suicidal ideation. Kelleher et al show in a large community sample that attenuated psychotic experiences were relatively common among young people who had a

diagnosis of moderate depressive disorder, and that the combination of experiences in this sample was significantly associated with suicidal behavior: i.e. patients did not need to present with severe depression or have formal psychotic symptoms to be at heightened risk[9]. In addition, depression has been linked to increased risk of transition from UHR to FEP, suggesting that in this group depression also indicates a poorer outcome[10]. However, the relationships are not straightforward nor is there sufficient evidence to suggest direct causality. In longitudinal studies depression and positive symptoms may co-occur but not necessarily predict each other over time[11].

Phenomenology of depression in schizophrenia: interplay of depression and negative symptoms

Depression is a mood disorder that is characterized by apathy, low mood and social withdrawal [12]. Beck describes a 'cognitive triad' in depression of "life is pointless, the future hopeless and the self is worthless"[13]. The nature of the phenomenology of depression in schizophrenia, however, has not often been interrogated in phenomenological terms. Some of our recent evidence suggests self-stigma, shame, difficulty in regaining trust in ones own thoughts after recovery from delusional beliefs, and poor motivation are core features rather than other more 'biological' symptoms such as early morning wakening, diurnal variation in mood or loss of appetite[14]. The Calgary Depression Scale for Schizophrenia (CDSS) is widely used to assess depression as a distinct from negative symptoms, with weight resting more on subjective reports of hopelessness, guilt and suicidal ideation rather than agitation, anhedonia and paranoid symptoms as seen in other depression rating scales[15].

Use of the CDSS has been built on the distinction between primary and secondary negative symptoms. Secondary negative symptoms (particularly those of such as anergia, alogia and flattened affect) may present as a result of depression[16]. However , there are features in common to both depression and negative symptoms, such as social withdrawal, diminished capacity to experience pleasure (anhedonia) and loss of motivation . With regard to anhedonia, recently there has been distinction between motivational anhedonia (motivation to pursue rewards) and consummatory anhedonia (pleasure experienced in anticipation or response to rewards). Consummatory anhedonia and difficulty in anticipating future pleasure may be more in keeping with depression, where as motivational anhedonia better seen as a primary negative symptom. Strauss and colleagues argue that anhedonia should not defined as a diminished capacity to experience pleasure but a cognitive dissonance of low pleasure that surfaces when a person is asked to report on future or past positive emotions, reduced pleasure seeking behavior or elevation of negative emotions[17]. This has strong similarities with depression at a symptom level (negative emotions associated with difficulty in retrieval of positive emotions or memories) and within the NIHR RDoC framework suggests the need to investigate anhedonia at a symptom level across diagnoses.

Thus, whilst anhedonia may be common to depression and negative symptoms, other core depressive symptoms, as assessed with the CDSS appear distinct. We have previously shown depression and negative symptoms as specifically assessed are orthogonal[2]. This leads to the possibility that whilst anhedonia itself may be considered transdiagnositc, subtypes including anticipatory, consummatory and motivational anhedonia, maybe more specific.

Depression and mood instability as a dimension of psychosis.
Of the many factor analysis studies of psychosis, all identify depression and more broadly mood symptoms as a distinct dimension, including those that investigate a schizophreniform sample in the absence of affective psychoes[18]. We note above the high rates of depression in UHR and first episode samples but importantly, *instability* of mood in the early course of psychosis is also widespread. Instability in mood and negative affect is associated with clinical and nonclinical paranoid thinking and with the emergence and persistence of auditory hallucinations[19]. It also explain new inception of paranoid ideas and auditory hallucinations at 18 months[20]. High rates of childhood trauma are reported in both schizophrenia and depression compared to controls and are thought to be important in the genesis of both disorders[21]. Mood instability may act as a mediator between traumatic events such as bullying and persecutory ideation as well as childhood sexual abuse and psychosis, though interestingly this effect doesn't hold true at the point of transition in UHR samples[22].

Psychotic-like experiences are also more common in individuals with anxiety and depressive disorders, while UHR samples have high rates of anxiety as well as depression[23]**.** Why mood instability levels are high in schizophrenia or how this relates to depression in this group requires further research, but the mechanism may involve maladaptive cognitive emotional regulation strategies involving situation selection, rumination, worry, re-appraisal and experiential avoidance. For example experience sampling method (ESM) studies demonstrate patients with schizophrenia are more stress reactive than first degree relatives or healthy controls, and this emotional reactivity correlates with positive symptoms and need for care[24].

The close linkage between psychosis symptoms and depression, especially in the prodromal phase has led to proposals that depression in schizophrenia may be the severe end of a dimension of affective dysregulation beginning in adolescence progressing into the early stages of psychosis as the illness crystalizes. Fusar-poli and Yung propose an increasing specificity and power of positive symptoms whereby at a population level both may be non significant co-occurrences, yet when seen in established severe mental illness have distinct specificity[25]. It is possible the relationship between mood and positive symptoms follow a similar course; thus when seen in UHR may represent non-specific indicator of pluripotent pathways, yet as illness progression occurs a more direct relationship is possible. Indeed with affective disorders, psychotic symptoms are understood to arise when mood symptoms are most severe, for example in psychotic depression, yet they often co-occur at population level and in UHR samples in a manner not specific to diagnostic categories[9]

Three pathways to depression in schizophrenia.
How are we to understand this varied picture of depression in schizophrenia? Birchwood argued that there are three distinct pathways: depression which is intrinsic to psychosis, depression which is a psychological reaction to the diagnosis and its implications for social status and position, and depression as 'smoking gun evidence' of historical childhood trauma [26]. This framework seems to have stood the test of time. Trauma, neglect and social adversity are now well established risk factors for schizophrenia[27]. These factors also share risk for a variety of other disorders (including depression itself) and for this reason depression may be trans-diagnostic. We have published a series of studies examining the second pathway[2, 26, 28-31]. The summary is that it is the way a person appraises the meaning and

significance of their psychotic experience, including their subordinate relationship to voices, or persecutors and the impact of the diagnosis on social status that underlies the development of depression. We have shown that this is the case even during the acute phases of illness where insight is not totally lost[2, 26]. Therefore, of Birchwood's three pathways it is the first, depression as intrinsic to psychosis itself, that may now need further exploration.

If we move to accept that depression, for some at least, is intrinsic in part to the disorder itself, the question arises as to whether this occurs as part of a Fould's hierarchy, whereby patients exhibiting symptoms at a given level must also display symptoms at each of the lower levels[32], whether depression a manifestation of their common aetiological factors, or indeed if there may be a more causal relationship. Recent evidence shows that first episode schizophrenia and first episode affective psychosis have similar changes in brain structure, although progressive insular grey matter loss may me more pronounced in schizophrenia[33]. Increase in stress reactivity seen in schizophrenia may be linked to inflammatory and structural brain changes[24]. Hippocampal grey matter volume (GMV) reduction is found in unipolar depression, related to the duration of illness[34] but is also seen in schizophrenia. Inflammation mediated effects on Brain derived neurotrophic factor (BDNF) is a proposed pathway for this effect[35]. There is evidence that changes in circulating inflammatory markers and neurotrophins associated with the onset of depression are also seen commonly in schizophrenia[36], with evidence that the presence schizophrenia and depression being specifically toxic; Noto recently demonstrated that IL-6, IL-4, IL-10 and TNFα were significantly higher in this patient group[37]. In addition, recent studies by Chuang et al show that in depression, blunted affect, alogia and withdrawal are inversely associated with grey matter volume in the bilateral cerebellum whilst in schizophrenia, anhedonia, and avolition are inversely related to white-matter volume in the left anterior limb of internal capsule and positively in the left superior longitudinal fasciculus and key areas involved in the processing of reward anticipation[38]. In functional brain imaging, patients with depression and schizophrenia show similarly enhanced brain response to fearful facial expressions, particularly in the thalamus, to those with affective psychosis[39]. Regions critical to emotional processing are common in models of psychotic symptoms and include the hippocampus, insula and prefrontal cortex. These areas are implicated in both depression with psychosis and schizophrenia[40]. In broader terms of affective instability, there is some convergence of evidence that alterations in amygdala activation is involved in difficulty in emotional processing, salience to emotional stimuli, and behavioural response[23].

Thus it is possible that depression (as a core dimension of psychosis) not only explains some of the commonality in biological findings across mood disorders and schizophrenia, but provides potential aetiological pathways. This may be particularly relevant when the most active illness process is ongoing i.e. during the early critical period when disease trajectories are set. We might suggest that depression drives forward further symptom dimensions through a stress-inflammation-structural brain change pathway. This area is ripe for further investigation.

Treatment of depression.

Even though depression in schizophrenia is increasingly recognised as a dimension of schizophrenia psychopathology, clinically it remains inadequately treated[41]. More than fifteen years have passed since Siris published "Depression in the era of

atypical antipsychotic agents' with the recommendation that antipsychotic dose reduction or changing to a atypical antipsychotic may reduce the occurrence of depression[42]. Yet the prevalence of depression in schizophrenia has remained high, and rates of suicide unaltered, despite the wide use atypical antipsychotics, suggesting more treatment options are needed.

Targeting the treatment of depression in early psychosis has the potential to reduce suffering, risk of suicide and improve functional outcome, yet the extent of the effectiveness of existing treatments for depression in the context of schizophrenia is unclear. CBT and anti-depressants are recommended in the treatment of unipolar depression and, in the recent update of the UK NICE guidelines for schizophrenia it is recommended this guidance be adhered to[43]; however, there is very little evidence for this assertion. Despite their frequent use on a pragmatic basis, there have been few sufficiently powered, randomised controlled trials of antidepressants for the treatment of depression in schizophrenia, although recent meta-analysis gives some limited evidence of effect[44]. Cognitive behavioural therapy for psychosis (CBTp) has been the subject of much research in recent years, however has primarily focused on effectiveness for positive symptoms, transition from high risk status and more recently on distress. No CBTp studies have used depression as a primary outcome or target of therapy. The pervasive presence of depression in schizophrenia and early phase psychosis, and the proposed role of affect dysregulation in the development of emerging psychotic thinking on the one hand and quality of life in established psychosis on the other, underlines the urgent need for treatment trials. We cannot assume that 'standard' pharmacological interventions or CBT for depression or would be effective. For example, as we have reviewed above, the content of depressive thinking in psychosis can include internalised stigma and entrapment by psychosis and intervention might therefore need to be augmented by practical steps to achieve mastery of the illness or of emancipating the individual from corrosive stigmatising stereotypes[2, 28].

Conclusion

There are probably several pathways to depression in schizophrenia, some of which are well understood. Depression in schizophrenia challenges a categorical and hierarchical diagnostic system. If we accept depression in schizophrenia is common, as our evidence would indicate, what are the implications for psychotic depression or schizoaffective disorder as diagnostic categories? This is open for debate, however, it is clear that the concept of depression as a comorbidity of schizophrenia is a misnomer; its role may well be much more profound. Depression is now recognized as occurring frequently in schizophrenia particularly as it develops in adolescence. It is significant in the prediction of transition to FEP, poor clinical outcomes, quality of life and suicide[1, 7, 8, 25]. Yet all this has not been translated into commensurate clinical recognition and to the resolution of uncertainties in therapeutic approaches. First episode psychosis sees the highest rate of decline in functioning, and high rates of depression, yet conversely it is a period of high level of recovery from positive symptoms. This underlines the need for focused interventions outwith positive symptoms. The interplay of depression and mood instability with the emergence of delusions and hallucinations, opens up the prospect of trials targeting affective dysregulation and mood instability as a preventive maneuver. The current lack of evidence for the treatment of depression in schizophrenia is the result of a lack of sufficient investigation, rather than lack of evidence of effect, and may result in a potential missed opportunity for effective intervention with potentially wide

consequences for the illness and its prevention. Trials of routine treatments for unipolar depression, with vs without adaption for the schizophrenia context should feature high on funders' research priorities as this holds the hope of a significant impact on recovery, reducing levels of completed suicide and patient suffering.

Acknowledgement
Max Birchwood is supported by the NIHR CLAHRC West Midlands+ initiative. This paper presents independent research and the views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

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