

Review Article

Prodrome in Psychiatry – An Epiphany

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A B S T R A C T

Prodromal symptoms in mental disorders develop weeks to months, even years, before the onset of the disorder. Most individuals manifest at least one prodromal symptom and seek medical help, but often the diagnosis is missed unless they present with complete symptoms indicating the onset of illness. As early identification and intervention at the prodromal stage can decrease the intensity or delay the progression of illness, knowledge about prodrome is mandatory.

Keywords: Prodrome, Psychiatry, Schizophrenia, Bipolar, Depression

Introduction

In the field of psychiatry, a 'cure' for psychotic disorders cannot be completely achieved most of the time. Hence, the identification of individuals at risk and early prevention by intervention is important to decrease the intensity of deficits. The origin of the concept of prodrome started way back when the period of subthreshold clinical signs and symptoms that individuals may undergo preceding the onset of psychosis arose first. In the 1640s, the term "a forerunner" was coined for this concept. Following this, various terms were introduced but finally, the French word "prodrome" paved the way for the term "a prodromal symptom" in 1834.¹ Underpinning this, Bleuler in 1911, was the one who had put forth the idea that the phase of changes in a person before developing schizophrenia can be labelled as a prodromal phase.² Chapman, in 1978, described that those disturbances can be in the dimensions of attention, speech production, thought block, perception,

and motor functions.³ The commonly accepted definition of prodrome was given by Keith and Matthews in 1991 as a "heterogeneous organization of behaviours temporally related to the onset of psychosis".⁴

Prodrome in Psychiatry

It is far common in clinical practice to stumble upon cases with a subthreshold clinical picture before they are identified as a complete disorder. Prodrome, in general, indicates the early signs and symptoms of illness that occur before the onset of the characteristic manifestations of the disease. In psychiatric disorders, there is initial prodrome where signs and symptoms occur before the first episode, whereas relapse prodrome refers to the symptoms and signs that warn the patient that an episode of the disorder may be triggered.³

Basically, the evolvement of prodrome has been described in two principal patterns. The first pattern is in which

the individual will undergo non-specific changes in mood like irritability towards noises, light and other sensations followed by which they will manifest with specific pre-psychotic symptoms like confusion and difficulty in concentration, and then they will develop psychosis. The second pattern is in which the individuals manifest specific changes in the earlier phase and neurotic symptoms as a result followed by the development of psychosis. Individuals with prodrome are categorised as individuals at risk mental state (ARMS) and ultra-high risk (UHR). At-risk individuals present with symptoms such as low mood, anxiety, and psychosis but may not necessarily meet UHR criteria whereas ultra-high risk (UHR) category individuals are those with symptomatic psychosis at risk state setting a high threshold to reduce misdiagnosis.³

Prodrome in Schizophrenia

Four of the six leading causes of the years lived with a disability are associated with neuropsychiatric disorders - one among them is schizophrenia which also has the highest monetary impact as per World Health Organization (WHO).⁵ The cause for this may be due to delayed onset of treatment due to a delay in the diagnosis. Intervening with medicine or psychotherapy can help in improving the consequences and have higher socio-occupational functioning when compared to those who have not had any intervention. As timely early interventions create an opportunity to postpone or lower the intensity of subsequent signs and symptoms, detection of prodrome is critical.

75% of the individuals having schizophrenia pass through various stages of prodromal symptoms and 1 in 4 of the high-risk sufferers convert to schizophrenia. 20%-40% of individuals who come under UHR criteria develop psychosis within 2-4 years, whereas 40%-50% develop within 1-2 years after the manifestation of prodromal symptoms. Research has shown that if intervened early, the relative reduction in the progression in 64% of people is at 6 months, for 55%, it is at 12 months, and for 42%, it is at 2-4 years.³

Subthreshold psychotic symptoms have been reported weeks, months, or even a year before the onset of the disorder and the non-specific mood changes much before this.⁶ Only a few go on to develop a complete psychotic disorder. The typical course of prodrome as evidence shows starts with negative or non-specific signs like melancholy and tension, social isolation, and academic/ occupational failure, followed by the start of basic symptoms like attenuated positive symptoms (APS), which will be intermittent, brief and of moderate intensity. Proximal to the development of psychosis, symptoms will be sub-psychotic like unusual thinking, perceptual abnormalities, and speech disturbances which is different from real psychosis as sub-psychotic symptoms occur once or twice a month, and last for a few minutes with less clear hallucinations or delusions.⁷ The

common age groups of the onset of prodromal symptoms are adolescents and young adults.⁸ Reportedly comorbid psychiatric illnesses are also common in this period where 30% have obsessive-compulsive disorder (OCD)⁹ and 12.5% have substance use disorder (SUD).¹⁰

Diagnosis can be done using various scales to evaluate prodromal symptoms like Structured Interview for Prodromal Symptoms (SIPS), Multidimensional assessment of psychotic prodrome, Bonn Scale for the assessment of basic symptoms, Comprehensive assessment of ARMS (CAARMS), Basel Screening instrument for Psychosis (BSIP), and Scale for prodromal symptoms (SOPS). These scales measure genetic risk, brief-limited psychotic symptoms, attenuated positive symptoms, and deterioration of symptoms over a given duration.³

Few investigations like elevation in biomarkers representing inflammation, oxidative strain, endocannabinoids, and glucocorticoids indicate high risk and as imaging studies have shown that structures involved could be bilateral cingulate cortex, frontal cortex and reduction in grey matter in cerebellar cortices, any changes in these regions of the brain in imaging of the individuals with prodromal symptoms should be intervened as they are at high risk to manifest with a full-fledged psychotic disorder. High-risk individuals should be identified and intervened appropriately which might halt the progression of aberrant neurodevelopmental processes.³

Cognitive behavioural therapy has been shown to be a promising intervention. It decreases symptoms, improves functioning, and decreases the rate of transition to psychosis. It also includes strengthening ideas, conduct tracking, schema testing, and coping capabilities. It was proven by studies that it mitigates the conversion risk to psychosis and this remission effect can be maintained for up to the following 4 years. Other therapeutic alternatives include family therapy, cognitive workup, supportive therapy, training in social skills, supported job opportunities or education.¹¹

Intervention with only a therapeutic approach and medication along with a therapeutic approach has shown the same results which imply the efficacy of a therapeutic intervention. Antipsychotic medications are effective but are preferably recommended when one does not respond to other modes of treatment or when an individual begins to manifest rapid and progressive debilitating signs of psychosis, indicating a potential psychotic break. If the need for antipsychotic medication arises, risperidone, olanzapine, and ziprasidone have shown promising results. Administration of omega-3 fatty acids at a dose of 1.2 grams per day versus placebo has shown a huge difference, favouring the therapy with omega-3 fatty acids.⁷ On the other hand, individuals with positive risk alleles if

treated with folate supplementation have shown a smaller number of relapses.¹² Drugs which act on the genetic variant val158met and drugs reducing catechol-o-methyl transferase activity if given at an early stage have shown development in the socio and occupational functioning.¹³

Prodrome in Bipolar Disorder (BD)

Historically, unipolar and bipolar depression were regarded as similar. However, they represent two distinct entities. Bipolar depression is much more likely to have psychotic features, diurnal mood variations, hypersomnia, leaden paralysis, psychomotor retardation, lability of temper, pathological guilt and deficits in sustained attention, verbal recall, verbal fluency, emotion-dependent cognitive processing while unipolar depression will have self-reproach, anergia, decreased libido, initial insomnia, weight reduction, low-interest levels, somatic complaints, a tendency to blame others, anxiety and deficits in impaired attention, mental processing speed, and mental flexibility.¹⁴

Early character or temperamental traits like irritable mood or dyscontrol behaviour in childhood may be predictors of the development of bipolar disease in the later stages. It could be observed that these traits are steadily increasing in number, frequency, and severity before the primary episode. These should be monitored intently. Every individual may have his or her own set of idiosyncratic caution signs. It will be useful for sufferers to create a "relapse profile" which includes potential triggers, early warning signs and symptoms, and prevention strategies.¹⁵

A protracted symptomatic prodromal period exists before the evolution of complete bipolar disorder, lasting for 9-12 years. Throughout the prodromal stage, there are three major clusters of syndromes which include hypomania/mania symptoms, prodromal depressive syndromes, and symptoms of attention deficit hyperactivity problems that are stated to be comorbidities in bipolar disorder with an occurrence of 22.5%. At least one episode of depression would have occurred before the first manic episode in 78.6% of sufferers and the remaining 21.4% would have manifested with the first hypomanic episode. An increase in frequency and quantity of alcohol was reported by 60% prior to the first episode of depression and 40.5% before the first hypomanic or manic episode. Prodrome in the offspring of parents with bipolar disorders (38%) is more common than prodrome in the offspring of healthy parents (17%).¹⁶ Assessments that are approved are early phase inventory for bipolar disorder criteria and bipolar prodrome symptom scale.¹⁷ The Bipolar Prodrome Symptom Interview and Scale—Prospective (BPSS-P) is a semi-structured interview developed based on DSM-4 criteria for BD. This scale consists of three main sections to evaluate mania, depression and general symptom index. It assesses the onset of the prodromal phase and the severity

of prodromal symptoms for the past one month and the past one year.¹⁸

Pharmacological treatment with mood stabilisers like lithium and valproate has not shown effectiveness. Regarding the monotherapy with antidepressants, study information is missing and the chance of inducing mania is more, however, under close monitoring, antidepressants can be administered according to guidelines. Others like physical exercise is shown to improve neurogenesis and neuroplasticity. As a delay in treatment is associated with worse social adjustment, suicide, increase in comorbidity rates, and greater hospitalisations, early intervention is mandatory.¹⁴

Psychoeducation plays a role in how to deal with stressful conditions and avoid them, if possible, for example, avoiding drastic lifestyle changes, taking on a task that necessitates being up all night for several nights, being wakeful till very late, drinking alcohol at events, and consuming drugs.

Family-focused therapy like psychoeducation with training in communication and problem-solving skills has proven to be associated with longer affective stability and milder symptoms. Outcomes are favourable with early family-targeted approaches, interpersonal and social rhythm therapy, and cognitive therapy based on mindfulness. All these have been shown to improve the symptoms, sleep patterns, emotional regulation, lowering anxiety, a longer period in remission, and better psychosocial functioning. A recent overview of psychotherapeutic interventions has shown promising results.¹⁹

Prodrome in Depression

Evaluating the prodromal phase of major depression has crucial implications pertaining to pathophysiological models of illness and relapse prevention. It could yield greater enduring outcomes with therapeutic efforts. Hence appraisal of prodrome in depression is important.²⁰

Theories Proposed

Helplessness theory as given by Martin Seligman stated that depression happens when someone learns that their attempts to escape bad situations make no difference.²¹ In an attempt to give attribution, Abramson and co-workers (1978) reformulated it as hopelessness theory stating that after a negative event, individuals who attribute it to inner, stable, global reasons have a greater chance of developing depression that is, they opine that the negative event is a result of their inadequate interpersonal ability (internal), which according to them will never change (stable), and will adversely impact all their other social interactions (global). Individuals who are emotionally susceptible tend to negatively associate stressful life events and loss of interpersonal relationships.²²

The duration of prodrome may vary from 1 to 19 weeks. It is believed that prior to the beginning of a depressed mood, all depressed patients have a minimum of one prodromal symptom. Mood instability like unanticipated and intense mood variations over a short and quick time is argued to be a precursor for depression. The most common prodromal symptoms reported are generalized anxiety (87%) and irritability (60%). Insomnia and reduced energy are also common symptoms.²³ There are a few gender differences in prodromal symptoms like females used to experience problems in concentration, hypochondriasis, fatigue, and distractibility, whereas, in males, psychic tension is a common symptom. Those who have a positive family history of depression have been reported to commonly manifest with irritability, concentration difficulty, and distractibility whereas, those with a negative family history manifest commonly with interrupted sleep, psychic tension, and stress.

Neurobiological correlates for depression were found to be an abnormality in amygdala and prefrontal cortex.²⁴ Proposed instruments for assessment are Clinical Interview for Depression and Related Syndromes (CIDRS)²⁵ and Paykel's Clinical Interview for Depression²⁶.

Prodrome in Mania

Several clinical characteristics could help predict that the individual is going to develop the first episode of mania as patients go through a phase of change in their mental state. Manifestations in more than half of patients during the 12 months before the onset of mania can be divided into the following categories: mood symptoms, change in sleep pattern, and behavioural changes or other symptoms.

With respect to mood, 50% of sufferers have progressing development in attenuated manic symptoms after which they progress to full-blown mania. 30% of patients initially develop depressive symptoms followed by the development of attenuated manic signs and symptoms, after which they progress into mania. 18% of sufferers develop attenuated manic symptoms after which they undergo depressive and hypomanic stages successively before entering into a full-blown mania. Sleep changes usually included disturbance in sleep in 83.3% and reduced duration of sleep or increased need for sleep in 61.1% of participants. Behavioural symptoms include increased stress, impaired functioning, and difficulty in concentration.²⁷ The majority identified disturbance in sleep (77%) as an indicator of prodrome of mania and other common symptoms were psychotic changes (47%), mood symptoms (43%), psychomotor change (34%), change in appetite (20%), increased anxiety (16%), and other symptoms (30%).²⁸ The duration of manic prodrome ranges from 1 to 120 days and a mean duration of 21 to 29 days which is shorter than for depression.²⁹

Risk factors and vulnerability markers along with these symptoms could denote impending first-episode mania. Risk factors include a family history of psychiatric illness and a history of experiencing traumatic events. Vulnerability markers are delayed development, traits of cyclothymia, previous history of depression, and a recent increase in levels of substance use. Instruments used are the Initial Mania Prodrome Questionnaire (IMPQ) and General Behaviour Inventory (GBI).²⁷

Prodrome in Obsessive Compulsive Disorder (OCD)

Most of the patients (93%) have reported at least one symptom of prodrome before the onset of the disorder. It is not necessarily of an obsessional kind as individuals have reported symptoms of phobia (53%), anxiety (29%), depression (19%), neurasthenic type (12%), and hypochondriacal type (11%).³⁰ Two main ways proposed for primary prevention of OCD are halting the genetic expression of OCD and through modification of environmental factors that might contribute to the expression of OCD. As strategies to halt genetic expression have not yet advanced to a level of being used therapeutically, we need to concentrate on modifying the environmental factors. Since early-life factors like physical abuse, negative emotions, insults during the perinatal period, poor motor development, personality or conduct problems predict the incidence of OCD, environmental factors during childhood are the target area of the investigation.³¹

Various approaches addressing environmental elements like the environment of family and parenting, particularly in kids of mother and father with OCD, prevention programmes that alter parenting styles, psychoeducation to reduce exposure of children to abnormal fear responses, creating extra-supportive family surroundings, and cognitive behavioural therapy in those with high ritualistic behaviour in ritualism which is a predictor of OCD. School teachers are usually aware of other common psychiatric disorders in childhood but not OCD. So, programmes to educate teachers deliver focused intervention to children who are at risk of developing OCD.³²⁻³⁴

Anti-inflammatory drugs have a potential therapeutic role as the inflammatory process contributes to the development of OCD.³⁵ Interestingly, Selective Serotonin Reuptake Inhibitors (SSRI), which are already in use as first-line drugs, have several immunological effects such as they reduce lymphocyte proliferation, alter cytokine secretion, and induce apoptosis. Drugs with anti-inflammatory properties, like minocycline, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), and atorvastatin, might show good results in the treatment of OCD.³⁶ Curcumin has also proven to be effective when tried on animals. However, there is no definite and conclusive evidence for any of the medications.³⁷

Conclusion

Prodrome is considered to be the crucial period to halt the progression or minimise the severity of the disorder. Hence there arises a need for early identification and prevention of the course of any disorder which if not done might decrease the quality of life of the affected individual. If individuals are intervened at an appropriate time, they might have a better outcome which makes the knowledge about prodrome mandatory.

Conflict of Interest: None

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