A broad clinical high risk mental state (CHARMS):

Methodology of a cohort study validating criteria for pluripotent risk

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Towards a pluripotent at-risk mental state

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Abstract

Aim

The development of the ultra-high risk (UHR) criteria for psychosis created a new paradigm for prevention research in psychiatry. Since a) prevention research faces the challenge of achieving adequate statistical power when focusing on single low-incidence syndromes and b) early clinical phenotypes are overlapping and nonspecific, this study broadens the UHR state beyond psychosis as an outcome. The CHARMS (Clinical High at Risk Mental State) study aims to prospectively validate a set of transdiagnostic criteria to identify help-seeking young people at risk of developing a range of serious mental illnesses.

Methods

This paper describes the methodology of the CHARMS study, which involves applying the CHARMS criteria to a cohort of help-seeking young people aged 12-25 attending youth mental health services in Melbourne. New referrals meeting the CHARMS criteria are allocated to the CHARMS+ group; referrals not meeting CHARMS threshold are allocated to CHARMS- group (control group); referrals meeting criteria for a full-threshold disorder are excluded. Transition status and clinical and functional outcomes are re-assessed at 6 and 12 months.

Conclusions

This study will be the first to introduce and validate clinical criteria to identify a broader 'at-risk' patient population, which may facilitate young people's access to clinical services and early treatment by reducing the reliance on 'caseness' defined according to current diagnostic categories being required for service entry. These new criteria may introduce a new, transdiagnostic approach for understanding risk factors and pathogenic mechanisms that drive the onset of severe mental illness and the next generation of preventive intervention trials.

Key words: at-risk mental state; clinical criteria; subthreshold states; pluripotent; transdiagnostic

Introduction

The development of the 'ultra-high risk' (UHR) for psychosis criteria more than 20 years ago created a new paradigm for prediction research and subthreshold intervention in psychiatry¹. However, research in the area has shown a reducing transition rate to psychosis²⁻⁴ and also a substantial rate of onset and persistence of non-psychotic disorders in the UHR population⁵⁻⁷. This presents a conceptual challenge but also the research problem of not having sufficient statistical power to identify predictors of psychotic disorder as an outcome and test preventive intervention strategies (by showing, for example, a reduced incidence rate of new cases)⁸. Indeed, many recent UHR intervention studies have suffered from lack of power due to a reasonably low rate of transition to psychosis, their primary outcome^{10, 11}. For example, both the EDIE-2 (early detection and intervention evaluation for people at risk of psychosis) trial and Neurapro trial showed modest 8%-11% transition rates over 12 months, which compromised the studies' ability to effectively test their respective interventions^{10, 11}. This issue has contributed to the proposal that prediction and prevention research should focus on high-risk groups with higher incidence rates and multiple risk factors^{8, 9}. As proposed by Cuijpers (2003), one way to achieve higher incidence rates is to target a *broad range of disorders* as outcomes of interest, and not be limited to a single relatively low incidence disorder such as schizophrenia.

Conceptually, this requires a broadening of the 'ultra-high risk' state and its operationalisation into a *transdiagnostic* at-risk mental state, which is also in line with evidence regarding the non-specific nature of emerging psychopathology. For example, the majority of UHR clients fulfil diagnostic criteria for one or more mood, anxiety, substance use and personality disorders, and the criteria capture markedly elevated risk for exit syndromes other than psychosis⁵⁻⁷. It has been argued that this may reflect an 'early shared pathway' or a form of *pluripotency* of the early clinical phenotypes of mental disorders^{12, 13}. That is, observed early signs and symptoms of mental ill-health may not indicate a fixed trajectory to particular diagnoses and may evolve into a range of different psychiatric syndromes^{12, 13}.

The concept of pluripotency of early clinical phenotypes also aligns with the clinical staging model of psychiatry¹⁴⁻¹⁶, which parallels staging models in general medicine (e.g., cancer). This model positions an individual along a continuum of illness which is defined according to stages: Stage 0 = no current

symptoms, Stage 1a = help-seeking with distress, Stage 1b = attenuated (i.e., sub-threshold) syndrome, Stages 2-4 = full threshold disorder with varying degrees of recurrence and severity. The staging model is also referred to as a 'trunk and branch' model, with the trunk representing the pluripotent risk of symptoms crystallising over time into particular syndromal branches, such as psychotic or affective disorders (see Figure 1) ¹⁴⁻¹⁶. This model allows for so-called comorbid outcomes, e.g. emergence of both psychotic and affective syndromes in a particular individual. This conceptual framework can guide the search for risk and protective factors for disease progression.

Clinical High at Risk Mental State (CHARMS) criteria

The study investigators developed a set of criteria to operationally define the early clinical phenotypes of a *range of exit syndromes*. The term "Clinical High At-Risk Mental State" (an adaption of the original "at-risk mental state" term¹⁷) is used to refer to this composite definition. These criteria, developed on the basis of available evidence and expert clinical experience, are operationalised using a combination of validated instruments (see Table 1). The CHARMS approach aims to identify the sub-syndromal population at risk of severe psychopathology, providing an operational definition of a broad-spectrum ultra-high risk or pluripotent state. In terms of clinical staging, CHARMS corresponds to Stage 1b ('attenuated syndrome').

We used subthreshold versions of specific disorders (i.e. psychosis, depression, mania, borderline personality disorder) as a basis for the CHARMS criteria because they provide useful late stage or 'end state' clinical phenotypes for which there are established treatment guidelines, but all of which have earlier stages with a need for care. Furthermore, global burden of disease data in young people aged 10-24 indicate prevention should focus on schizophrenia, unipolar depression and bipolar disorder, given that these disorders contribute the largest burden of disease in this age group¹⁸. Given that Borderline Personality Disorder is a common and significantly impairing disorder amongst this age group and is associated with help-seeking behaviour, it was also included as a target syndrome in the criteria¹⁹.

However, the proposed criteria (and chosen exit syndromes) are preliminary and the associated thresholds may not yet be valid or precise, and therefore require thorough empirical investigation. Therefore, we designed an observational study with the following aims:

- (1) To prospectively establish the predictive and discriminant validity of the CHARMS criteria in a cohort of help-seeking young people meeting CHARMS criteria and a comparison control group.
- (2) To identify clinical predictors of progression to full threshold syndromes, including anxiety, stress, sleep disturbance, general psychopathology, functioning, substance abuse, maladaptive personality traits and cognitive biases.

This paper presents the study design and methodology of the CHARMS study.

Methods

The CHARMS study adheres to ethical principles as formulated in the Declaration of Helsinki and is performed according to ICH-Good Clinical Practice (GCP). The study was approved by the local ethics committee (Melbourne Health Human Research Ethics Committee, #HREC/15/MH/276) and participants provide written informed consent prior to study enrolment. For participants under 18 years of age, parental consent is also obtained.

Design

The CHARMS study is a longitudinal study, involving 160 participants who meet CHARMS criteria ('CHARMS+') and 160 controls ('CHARMS-'). The control group comprise young people with symptoms not reaching CHARMS criteria threshold. Assessment points are at baseline, 6 and 12 months.

Sample and setting

Potential participants are help-seeking young people aged 12-25 who are referred to Orygen Youth Health (OYH) or one of four *headspace* clinical centres in Melbourne, Australia. OYH is a multi-component State Government funded mental health program for young people in western metropolitan Melbourne. The four *headspace* centres, located in the suburbs of Sunshine, Glenroy, Werribee and Craigieburn, provide universal access under a Federally-funded model of enhanced primary care to a broad array of mental health and welfare services. Inclusion criteria are: (i) Ability to give informed consent, (ii) help-seeking, and (iii) between the ages 12-25 years. Exclusion criteria

are: (i) documented history of intellectual disability, and (ii) current of past full threshold (Stage 2) disorder (psychosis, bipolar disorder, severe major depressive disorder, borderline personality disorder).

Procedure

Recruitment commenced in April 2016 and is expected to be completed in April 2018. In consultation with the relevant clinical teams, young people referred to OYH or headspace are approached by a research assistant (RA) in person or via telephone to discuss the aims of the study and their interest in participating. When a young person is interested and informed consent is obtained, a baseline interview is scheduled. During this baseline interview, the CHARMS criteria are formally assessed. If a participant *exceeds* the threshold for the CHARMS criteria (i.e. presents with a full threshold disorder), the participant is excluded from the study and the assessment is discontinued. If the participant meets the CHARMS criteria ('CHARMS+') or falls below the CHARMS threshold ('CHARMS-'), he/she is included in the study. After the structured interview conducted by the RA, the self-report measures are completed by the participant using an iPad. The duration of the baseline interview is approximately 2-3 hours.

Study participants are re-assessed at 6 and 12 months using the same interview measures and test battery with a few exceptions (see Table 2). For participants unable to attend a face-to-face follow-up interview, a telephone interview is administered. If participants are unable to be re-interviewed, their diagnostic status at last clinical contact is sourced from medical record files and state medical records.

RA's are trained by experienced researchers and clinicians on the Chief Investigator team. Inter-rater reliability will be established during the course of the study.

Measures

Table 1 presents a detailed description of the ascertainment of CHARMS criteria using the following four interview measures (CAARMS, SCID-5, QIDS-C, SOFAS).

Interview measures

*Comprehensive Assessment of At-Risk Mental States*²⁰ (CAARMS). The CAARMS is a semi-structured interview which was developed to identify help-seeking young people who are at UHR for psychosis²⁰. The full version of the CAARMS includes seven domains: positive symptoms, cognitive change/attention, emotional disturbance, negative symptoms, behavioural change, motor/physical changes, and general psychopathology²⁰. Each domain in the CAARMS receives a global rating score (0–6), a frequency score (0–6) and pattern of symptoms with substance use score (0–2). The positive scale also includes an additional distress score (0–100).

*Structured Clinical Interview for DSM-5*²¹ (SCID-5) and the *Structured Clinical Interview for DSM-5 Personality Disorders*²² (SCID-5-PD). SCID-5 and SCID-5-PD are semi-structured interviews for systematically establishing clinical diagnoses based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition²³. The SCID-5 is considered the "gold standard" in generating clinical diagnoses. Of the SCID-5-PD, only the borderline personality disorder module (BPD) and schizotypal personality disorder module (SPD) are assessed, which correspond to the modules used in SCID-IV²⁴.

*Quick Inventory of Depressive Symptomatology – Clinician rated*²⁵ (QIDS-C). QIDS-C is a clinician-rated 16-item questionnaire which assesses the severity of depressive symptoms during the previous week. All QIDS items are weighted on a 4-point Likert scale (0–3) with a higher score reflecting increasing symptom severity.

*Social and Occupational Functioning Scale*²⁶ (SOFAS). SOFAS is an observer-rated scale that assesses social and occupational functioning on a 0–100 scale.

*Global Functioning Scale: Social*²⁷ (GFS) and *Global Functioning Scale: Role*²⁸ (GFR). GFS and GFR are complementary scales derived from the traditional GAF format. The GFS assesses quantity and quality of peer relationships, level of peer conflict, age appropriate intimate relationships, and involvement with family members. The GFR assesses age appropriate performance in school, work,

or home duties. Both scales are rated using a 1 (extremely dysfunction) to 10 (superior functioning) scale.

*Young Mania Rating Scale*²⁹ (YMRS). YMRS contains 11 clinician-rated items that assess severity of manic symptomology over the previous 48 hours. Each of the 11 items are anchored by five specific symptom severity descriptions. The YMRS is considered the 'gold standard' of mania rating scales³⁰.

Self-report measures

*Depression Anxiety Stress Scale-21*³¹ (DASS-21). DASS-21 is a short version of the 42-item DASS. It is a dimensional self-report scale designed to measure negative emotional states of depression, anxiety, and stress. The scale has 21 items for these three scales with 7 items each. Responses are rated on a 4-point scale that measures how much each item applies to the respondent over the past week. The DASS-21 has demonstrated good psychometric properties³²; however, when administered in children and adolescents, only one (general) component is extracted³³.

*Bipolar Spectrum Diagnostic Scale*³⁴ (BSDS). BSDS is a narrative-based scale which assesses the entire bipolar spectrum, gathering hypomania or subthreshold manic states. The BSDS has been demonstrated to be an efficient self-rating scale with excellent sensitivity, making it useful in detecting subthreshold states of bipolar illness^{34, 35}.

Personality Inventory for DSM-5, Brief version^{36, 37} (PID-5-BF). PID-5-BF assesses the recent maladaptive personality trait model proposed in DSM-5 (Alternative Model of Personality Disorder, AMPD). This 25-item version is intended as a screening instrument for personality pathology in adults and adolescents. The PID-5-BF measures five maladaptive traits (Negative Affectivity, Detachment, Antagonism, Disinhibition, and Psychoticism) using 5 items for each trait. Two recent studies on the psychometric properties of the PID-5-BF suggest that the PID-5-BF is a reliable screening tool of DSM-5 AMPD maladaptive traits^{38, 39}.

*Davos Assessment of Cognitive Biases Scale*⁴⁰ (DACOBS). DACOBS aims to measure four cognitive biases specific to positive symptoms of psychosis (jumping to conclusions, belief inflexibility, selective attention for threat, external attribution bias), two cognitive limitations (social cognition problems, subjective cognitive problems) and avoidance behaviour. It has a total of 42 items scored on a 7-point Likert scale with a two-week time frame. The DACOBS has demonstrated excellent reliability (Cronbach's alpha = .90)⁴⁰, good internal consistency, and convergent validity⁴¹.

*Munich Chronotype Questionnaire (MCTQ)*⁴². MCTQ quantitatively assesses 'chronotype', which refers to individual differences in the timing of sleep within the 24-hour day. The MCTQ assesses information on sleep and activity separately for work and work-free days, thereby obtaining chronotype based on the midpoint between sleep onset/offset on free days corrected for oversleep (as a result of sleep debt accumulated during work days)⁴³.

*Insomnia Severity Index*⁴⁴ (ISI). The ISI assesses the severity of both nighttime and daytime symptoms of insomnia. It has a total of 7 items rated on a 4-point Likert scale that assess sleep-onset and sleep maintenance difficulties, satisfaction with sleep pattern, interference with daily functioning, impairment attributed to the sleep problem and degree of distress caused by these difficulties. The ISI has been demonstrated to be a reliable and valid instrument to assess insomnia in the adult^{44, 45} as well as adolescent population⁴⁶.

Statistical Analyses

Power

There are two primary aims of this study. One is to compare the transition rates of the CHARMS+ (expected transition rate 20%) and CHARMS- (expected transition rate 3%) groups. Allowing for a 20% drop-out rate (based on previous UHR research), at 5% significance level we would require 76 CHARMS+ and 152 CHARMS- individuals in order to have 80% power. A larger sample size is required for CHARMS- because the expected transition rate for this group is very low (3%) requiring a larger sample for a greater number of transitions in order to achieve adequate power. The other aim is to

estimate the transition rate of the CHARMS+ group. We plan to recruit 160 individuals for this group which would give us a reasonable precision of $\pm 7\%$ for the estimation with a 95% confidence level. Deriving a sample to address the two aims together and rounding up the numbers, requires a total sample size of 320 (160 for each group).

Data analysis

The Kaplan-Meier method will be used to estimate the rate of transition to Stage 2 disorder for the CHARMS+ and CHARMS- groups. Cox regression will be used to test for the difference in hazard rate between the two groups and also to explore potential predictors of progression to Stage 2 disorders. Overlap in the outcomes of interest (e.g., a participant who transitions to full-threshold psychosis and also to severe major depression) will not present a problem statistically or conceptually, as we are concerned with transition to and prediction of any Stage 2 'exit syndrome', rather than specific exit syndromes. Multilevel regression will be used to compare the groups on continuous outcomes at 6 and 12 months and to investigate the association between baseline risk factors and 6 and 12 month symptomatic/functional outcome in CHARMS+.

Discussion

This paper presents the study methodology of the CHARMS study, the first empirical investigation of a novel transdiagnostic set of clinical criteria for prospectively identifying young people at-risk of developing a range of serious mental illnesses. By building on previous UHR criteria and focusing on transdiagnostic characteristics of mental illness, increasing incidence rate and statistical power, this study may introduce a new, more powerful paradigm for patient identification and investigation of the mechanisms of disorder onset.

Testing and validating this broader set of at risk-criteria recognises the heterogeneity of pathways and outcomes for young people with sub-syndromal psychopathology and opens the door to trialling preventive interventions in this group (e.g., psychosocial interventions, acetylcysteine, neuroprotective agents such as omega-3 fatty acids) that are proportionate to presenting problems and which may be effective in delaying or preventing a range of serious mental illnesses.

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Table 1 CHARMS criteria

Subgroup	Instrument	Description
Psychosis trait vulnerability group	FHI, SCID-5-PD, SOFAS	Family history of psychosis in first degree relative OR Schizotypal Personality Disorder AND SOFAS score of 50 or less for <i>over 12 months</i> OR SOFAS score at least 30% below previous level
Bipolar trait vulnerability group	FHI, SCID-5	<u>Depression + Cyclothymic features / Genetic Risk Group:</u> Depression: For <i>at least 1 week</i> : depressed mood, or loss of interest or pleasure and at least 2 criteria from the list: (1) significant weight loss, (2) insomnia or hypersomnia nearly every day, (3) psychomotor retardation or agitation, (4) fatigue or loss of energy, (5) feelings of worthlessness or excessive or inappropriate guilt, (6) diminished ability to think or concentrate, (7) recurrent thoughts of death, recurrent suicidal ideation. The episode (a) cannot be due to the direct physiological effects of a substance or condition (b) doesn't need to cause a clinically significant drop in functioning. AND Cyclothymic features: For a <i>minimum of 6 months</i> (lifetime) high and low mood (no more than 2 consecutive months without symptoms) and at least 3 criteria from the list: (1) decreased need for sleep (e.g. feels rested after only three hours sleep), (2) increased energy, (3) inflated self-esteem or grandiosity, (4) increased goal directed activity, (5) restlessness, (6) more talkative than usual or pressure to keep talking, (7) unusual ideas, clear thinking (8) troublesome behaviour (9) inappropriate sense of humour. The episode (a) cannot be due to the direct physiological effects of a substance or condition and (b) doesn't need to cause a clinically significant drop in functioning. OR Genetic risk: First degree relative with bipolar disorder.

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Attenuated psychotic symptoms group	CAARMS	<p>Intensity: Global Rating Scale Score of 3-5 on Unusual Thought Content subscale, 3-5 on Non-Bizarre Ideas subscale, 3-4 on Perceptual Abnormalities subscale and/or 4-5 on Disorganised Speech subscales (symptoms present for <i>at least one week in the last year</i>) AND Frequency: Scale Score of 3-6 on Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities and/or Disorganised Speech subscales</p> <p style="text-align: center;">OR</p> <p>Intensity: Global Rating Scale Score of 6 on Unusual Thought Content subscale, 6 on Non-Bizarre Ideas subscale, 5-6 on Perceptual Abnormalities subscale and/or 6 on Disorganised Speech subscales (symptoms present for <i>at least one week in the last year</i>) AND Frequency: Scale Score of 3 on Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities and/or Disorganised Speech subscales</p>
Attenuated (hypo)manic symptom group	SCID-5	<p>A distinct period of abnormally and persistently elevated, expansive or irritable mood and ≥ 2 (3 if irritable) of the following 'B' criteria for at least 2 days: Inflated self-esteem or grandiosity; decreased need for sleep (e.g. feels rested after only three hours sleep); more talkative than usual or pressure to keep talking; flight of ideas or subjective experience that thought are racing; distractibility; increased goal directed activity (either socially, at work, or sexually) or psychomotor agitation; excessive involvement in pleasurable activities which have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)</p> <ol style="list-style-type: none"> The duration of this period can be maximal 3 days if <ul style="list-style-type: none"> ≥ 3 'B' criteria are met (≥ 4 if irritable) and it is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic (criterion 'C'); and the disturbance in mood and the change in functioning is observable by others (criterion 'D'). The duration of this period can be maximal 6 days if: <ul style="list-style-type: none"> ≥ 3 'B' criteria are met and 'C' or 'D' ≥ 3 'B' criteria are met and neither 'C' or 'D' are 2 B criteria in any combination with 'C' and 'D' The episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment)

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Moderate (Attenuated) depression group	SCID-5, QIDS-C	<p><u>Major Depressive Episode (current or past)</u> For <i>at least 2 weeks</i>: depressed mood, or loss of interest or pleasure + at least 5 criteria from the list: (1) significant weight loss, (2) insomnia or hypersomnia nearly every day, (3) psychomotor retardation or agitation, (4) fatigue or loss of energy, (5) feelings of worthlessness or excessive or inappropriate guilt, (6) diminished ability to think or concentrate, (7) recurrent thoughts of death, recurrent suicidal ideation. The MDE must also: (a) not be due to the direct physiological effects of a substance, (b) cause a clinically significant drop in functioning and (c) not be better accounted for by bereavement.</p> <p style="text-align: center;"><u>AND</u></p> <p>Current QIDS Score: 11-15</p>
Attenuated borderline personality group	SCID-5-PD	<p>For <i>at least 6 months</i>: at least 2 but less than 5 criteria from the list: (1) frantic efforts to avoid real or imagined abandonment (2) a pattern of unstable and intense interpersonal relationships characterised by alternating between extremes of idealization and devaluation (3) identity disturbance: markedly and persistently unstable self-image or sense of self (4) impulsivity in at least two areas that are potentially self-damaging (e.g. spending, sex, substance abuse, reckless driving, binge eating). This does not include suicidal or self-harming behaviour (5) recurrent suicidal behaviour, gestures, or threats, or self-mutilating behaviour (6) affective instability due to a marked reactivity of mood - intense feelings that can last from a few hours to a few days (7) chronic feelings of emptiness (8) inappropriate intense anger or difficulty controlling anger (9) transient, stress-related paranoid ideas or severe dissociative symptoms.</p>
Brief limited intermittent psychotic symptom (BLIPS) group*	CAARMS	<p>Intensity: Global Rating Scale Score of 6 on Unusual Thought Content subscale, 6 on Non-Bizarre Ideas subscale, 5 or 6 on Perceptual Abnormalities subscale and/or 6 on Disorganised Speech subscales (symptoms present for <i>less than one week in the last year</i>) AND Frequency: Frequency Scale Score of 4-6 on Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities and/or Disorganised Speech subscales</p>

FHI = Family History Index [Orygen]; SCID-5= Structured Clinical Interview for DSM-5; SOFAS=Social and Occupational Functioning Scale; CAARMS=

The Comprehensive Assessment of At-Risk Mental States; QIDS - C= Quick Inventory of Depressive Symptomatology – Clinician rated; SCID-5-PD= Structured Clinical Interview for DSM-5 Personality Disorders

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Table 2. Schedule of Assessments

	VISIT NUMBER	1	2	3
	Assessment	Baseline	Month 6 (± 2w)	Month 12 (±2w)
Background	Informed Consent	X		
	Demographics, medical &	X		
	Present/past treatment	X	X	X
	FHI	X		
Interview	CAARMS	X	X	X
	SCID-5	X	X	X
	SCID-5-PD*			
	QIDS-C	X	X	X
	SOFAS	X	X	X
	GFS/GFR	X	X	X
	YMRS	X	X	X
Self-report	DASS-21	X	X	X
	DACOBS	X		
	PID-5-BF	X	X	X
	BSDS	X		
	Sleep Questionnaire	X	X	X

FHI = Family History Index [Orygen]; CAARMS= The Comprehensive Assessment of At-Risk Mental States; SCID-5= Structured Clinical Interview for DSM-5; SCID-5-PD= Structured Clinical Interview for DSM-5 Personality Disorders; *Borderline personality disorder module and schizotypal personality disorder module; QIDS - C= Quick Inventory of Depressive Symptomatology – Clinician rated; SOFAS=Social and Occupational Functioning Scale; GFS= Global Functioning Scale: Social and GFR= Global Functioning Scale: Role; YMRS= Young Mania Rating Scale; DASS-21 = Depression Anxiety Stress Scale (21 items version); DACOBS= Davos Assessment of Cognitive Biases Scale; PID-5-BF= The Personality Inventory for DSM-5, Brief Version; BSDS= Bipolar Spectrum Diagnostic Scale; Sleep Questionnaire= Insomnia Severity Index and Munich ChronoType Questionnaire.

Figure Legends

Figure 1. Illustration of the clinical staging model for mental disorders.

figure 1[4]_converted.eps

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