Deconstructing depression: unified syndrome or groups of symptoms?

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Chapter 1

General Introduction

1.1 Preface

Depression has known many definitions over the course of time. Depression first appeared in writing in Mesopotamia in circa 1792 BC and was considered to be a consequence of demon possession causing distress, abnormal behavior and suicide [1]. Since then, our thoughts about cause and consequences of depression have drastically changed and depression is recognized today as a common, debilitating medical illness that affects how one feels, thinks and acts. Depression is described as a disorder in which the patient experiences feelings of sadness and/or a loss of interest in activities once enjoyed. It can lead to a variety of emotional and physical problems and impairs a person's ability to function at work and at home.

Depression is a substantial public health problem with a heavy burden for the patient, his/her caregivers and society [2-4]. It remains a disease with one of the highest burden, expressed in number of Disability Adjusted Life Years (DALY's; [5, 6]). A staggering 18.7% of the Dutch population has had a depression before the age of 65 [7]. Its economic impact is immense; the estimated cost to global economy is about 1 trillion euro in lost productivity per year [6, 8].

Over the past decades, much research has been conducted regarding its etiology, clinical characteristics, treatment, and course [9, 10]. Evidence-based guidelines for depression treatment have been developed consisting of psychotherapy (e.g. Cognitive Behavioural Therapy [CBT], interpersonal therapy [IPT]), pharmacotherapy (e.g. tricyclic antidepressants [TCA], selective serotonin reuptake inhibitor [SSRI]), or both [11]. These treatments are sufficient for the majority of patients, 50% of depressed patients recovers within 6 months and 76% recovers within 12 months. However, a substantial 20% suffers a chronic course and does not recover within 24 months, and a recurrent course is common [12].

One of the main challenges when researching or treating depression, has been the vast heterogeneity in etiology, symptomatology, and course of depression [13]. Two patients who both meet criteria for major depressive disorder (MDD) may have only few overlapping symptoms. For example, patient "A" is a 70 year old female who experienced psychotic symptoms of guilt, feelings of worthlessness, and a depressed mood. These symptoms started a few months after the loss of a loved one. She experienced exceeding psychological distress, but fortunately recovered with medical treatment within three months. Patient B is a 40 year old male who experienced less severe symptoms, mostly consisting of low energy,

psychomotor retardation and anhedonia. His symptoms were related to somatic problems, which despite treatment lasted for more then two years.

Given this heterogeneity, one may wonder whether depression actually constitutes a single unified disorder. Alternatively, it may be considered that not depression as a syndrome should be the topic of research but rather depression as a constellation of separate individual symptoms that together form the disease state of depression. Individual symptoms may have different risk factors and course trajectories, which remain unnoticed when depression is being researched as a unified syndrome. This heterogeneity formed the starting point for the present dissertation, which focuses on the separate symptoms of depression.

1.2 Diagnosing mood disorders and measuring symptom severity

Already in 1959, Karl Gustav Hempel wrote about the need for a progression from descriptive towards an explanatory classification in psychiatry [14]. Despite major research efforts during the past 70 years, this has not yet been achieved. Instead, disorders are "diagnosed", or rather classified, based on criteria that can be checked off by clinicians and researchers. Based on the Diagnostic and Statistical Manual of Mental Disorders, currently in its Fifth Edition (DSM-5), Major depressive disorder is a mood disorder that consists of at least five out of nine symptoms as presented in Table 1, of which a *depressed mood* or *anhedonia* (diminished interest or pleasure) must be present for at least two weeks. Classifications are mainly descriptive and with a few notable exceptions, such as post-traumatic stress disorder (PTSD), causal frameworks are excluded from the DSM classification [15]. Using this approach, disorders are classified regardless of underlying causality.

Table 1. DSM-5 criteria
Major depressive disorder (MDD)
Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
• Depressed most of the day, nearly every day as indicated by subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful) • Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by subjective account or observation) • Significant weight loss when not dieting or weight gain (e.g., change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day • Insomnia or hypersomnia nearly every day • Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down) • Fatigue or loss of energy nearly every day • Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick). • Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others) • Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
The episode is not attributable to the physiological effects of a substance or to another medical condition.
The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
There has never been a manic episode or a hypomanic episode.

Many psychiatric disorders cannot be sharply distinguished from each other, and disorders often seem to overlap, suggesting a shared etiology. DSM-5 classification is based on clinical consensus and does not assume that its categories represent distinct clinical entities with absolute borders [15]. Especially anxiety and depressive disorders often co-occur. There is a lifetime comorbidity between the two disorders of 43.6% for men and 55.8% for women [16].

These disorders can be treated with the same pharmacological interventions and have overlapping risk factors [17]. One can speculate if it is reasonable to approach mood- and anxiety disorders as two distinct entities. During the development of the DSM-5 and International Classification of Diseases, 11th version [ICD-11; 18], Goldberg, Krueger [19] stated that "*Mixed presentations of mood- and anxiety disorders may be the norm*".

Despite these difficulties, the DSM-5 could be considered a dictionary of mental disorders. It is of value that researchers and clinicians at least share a common international language, and that patients are classified by clinicians according to the same diagnostic criteria [20]. However, field trials demonstrated questionable (interrater) test-retest reliability of MDD with a kappa of 0.25 (95% confidence interval [CI]: 0.13–0.36). This was substantially lower than the other classifications that were assessed, such as borderline personality disorder (kappa: 0.34; 95% CI: 0.18–0.51) and alcohol use disorder (kappa: 0.40, 95% CI: 0.27–0.54) [21].

Another way of measuring depression and anxiety is by using self-report symptom measures. Self-report questionnaires are frequently used in mental healthcare to measure the severity and course of psychiatric disorders. The general format of self-report questionnaires is that frequency and severity of individual symptoms are scored with ordinal items, which are equally weighted and summed. These sum scores are thought to reflect the severity of the psychopathology and can be used as a tool for quantifying the patient's experienced symptoms. Hereby, self-reported measures can assist a clinician in the initial evaluation of patients [22], and when administered repeatedly, to monitor the effect of treatment [23]. Self-report questionnaires can be used to measure the general psychological distress/psychopathology [e.g., 48-item Symptom Questionnaire; SQ-48; 24] or symptoms of specific disorders such as depression [e.g., Inventory of Depressive Symptomatology self-report; IDS-SR; 25] or anxiety/fear [e.g., Beck's Anxiety Inventory; BAI; 26; Fear Questionnaire; FQ , 27].

1.3 Symptoms versus syndromes

A syndrome is defined by the Cambridge dictionary as *"a combination of medical problems that shows the existence of a particular disease or mental condition"* [28]. Most research thus far has focused on depression as a syndrome, assuming a single underlying disorder or construct [e.g. 26, 29, 30]. In this line of thought, individual symptoms are reflections of the

underlying latent depression construct or disease. When the disease severity declines, one assumes that the severity of its individual symptoms would also decline more or less together. The line of reasoning is similar to any medical disease, where it is assumed that symptoms improve as the underlying causal disease entity resolves. This model works rather well for other diseases, such as COVID-19 where symptoms of fever, coughing, stuffy nose and loss of smell and taste are a direct reflection of the underlying viral infection. Subsequently, when the SARS-CoV-2 virus infection has successfully been defeated by the immune system, COVID-19 symptoms generally resolve, although sometimes more permanent damage may continue. However, these assumptions may be problematic when it comes to depression. Although the SARS-CoV-2 virus can directly be measured as the pathological agent, this is not the case for depression. Moreover, although the nine main symptoms of depression correlate with each other, depression has highly different presentations among individuals and it seems unlikely that depression symptoms are interchangeable measurements of one latent construct of depression [31].

Depression symptomatology show substantial variability among individual patients, but also within the same person over time. Studies that did assess symptom-specific course trajectories have shown important average differences among the trajectories of individual symptoms. Symptoms differ in their response to treatment, with sleep problems, energy loss, and cognitive problems most often reported as showing a residual (and potentially pre-existing) course[32-37]. This is something that one would not expect if these symptoms are (equally) related to one underlying depression syndrome. If these symptoms would reflect one underlying latent disorder, they would demonstrate a more or less synchronized decrease when the patient would recover from the underlying disorder. Given the heterogeneous nature of depression it can be doubted whether depressive disorder, or at the same token anxiety disorders, do in fact exist as unified latent syndromes.

Multiple attempts for constructing more homogeneous subtypes of depression have failed. The proposed subtypes have been based on symptom profiles (melancholic depression, psychotic depression etc.[38]); etiologically-based (early trauma depression, organic depression, drug induced depression, etc.); time of onset-based (early and late onset depression, seasonal depression, etc.); treatment resistant depression subtype; symptom severity (mild, moderate, or severe); or several biology driven subtypes [39, 40]. In fact, a

meta-review of 754 reviews published between 2000 and 2011 identified 15 commonly used subtypes of major depressive disorder. Despite the vast amount of literature about this subject, no clear differences in clinical presentation or long-term outcomes between the different subtypes can consistently be replicated [39, 41]. Moreover, although the different subtypes attempt to overcome the non-specificity of major depressive disorder, no differential impacts of causes and treatments are found [40]. Rather, focusing on (the complex relationships among) individual symptoms may be our way forward [42-44].

Individual symptoms can be conceived as separate entities that may each have their own (genetic) etiology [45, 46]. This idea has been supported by evidence of a population based twin registry (3084 pairs), which found that major depressive disorder did not reflect a single dimension of genetic liability [47]. Instead, three underlying dimensions were found that index genetic vulnerability for cognitive/psychomotor, mood, and neurovegetative symptoms. Though replication is needed, this suggests that individual symptoms (or symptom domains) may have separate genetic etiology.

Although related to, but not entirely within the scope of the present dissertation, there can also be causal relationships between individual symptoms. Within the field of psychiatry and clinical psychology, this is also known as the *network-theory*. For example, sleeping problems may cause low energy, which in turn may cause concentration problems. Or feelings of worthlessness and guilt cause a depressed mood which causes anhedonia which eventually causes suicidal ideations. This explains why depression as a syndrome can have different etiologies among patients, although individual symptoms may be correlated to each other. Taken together, it can be fruitful to study depression not as a distinct unified syndrome or latent construct, but rather as a heterogeneous group of loosely related symptoms.

1.4 Predicting the course of depression and anxiety

Improving the ability to predict the onset and course of mood and anxiety disorders is of clinical relevance for prevention, early detection, staging, and personalized treatments [48]. However, despite a large body of epidemiological research, the course and onset of mood and anxiety disorders remain difficult to predict.

Several studies demonstrated that individual symptoms also may have different risk factors [49-52]. In a comprehensive study by Lux and Kendler [53], the relation between 25 risk

factors (including demographics, psychiatric history, personality and life events) and the nine DSM symptoms of depression were analysed. The relationships proved surprisingly complex. Some risk factors proved to have a specific relation to certain symptoms, other "risk" factors could be positively associated to some symptoms but negatively to others. If all depressive symptoms are caused by an underlying disorder, symptoms are expected to have similar risk factors because risk factors are supposed to influence the liability to develop depression, not specific symptoms [54]. However this is not the case, suggesting that research on depression risk could benefit from a symptom-specific approach instead of focusing on depression as a syndrome.

Several predictive variables have been established for predicting the onset and course of depression and anxiety [e.g., 55, 56]. These variables include demographic characteristics (e.g. gender, age, and socioeconomic status), clinical characteristics (e.g. symptomatology and preceding course), personality characteristics (e.g. neuroticism and personality psychopathology), and biological variables (e.g. somatic disease and inflammation). In the present dissertation, we researched the predictive values of preceding chronicity, personality traits, inflammation and how these relate to the individual symptoms of depression. Moreover, we assessed if more advanced statistical methods could improve the accuracy for predicting the onset and course of depression and anxiety.

1.4.1 Psychiatric history: preceding chronicity

The preceding course is one of the most important predictive factors for depression. Acknowledging the Importance of a preceding depressive course led to the addition of persistent depressive disorder (i.e. a combination of dysthymia *and* chronic depression) in the DSM-5 [57]. Patients meet the criteria of this disorder when they experience a depressed mood for most of the day, for more days than not, for at least 2 years. When patients experience a depression for two years or more, they are likely to have an unfavourable course in the future. In this way, chronic depression forms one of the strongest prognostic predictors [58]. A previous analysis in the Netherlands Study of Depression and Anxiety (NESDA) demonstrated that depression persisted over the course of 4 years in 53% of the patients with chronic depression at baseline versus 27.8% of patients with nonchronic depression at baseline; which is consistent with findings from others [55, 58-62]. It is currently unknown

whether chronicity affects the course of all symptoms equally, or rather individual symptoms at varying magnitudes.

1.4.2 Personality: traits as prognostic factor

Personality pathology (PP) is another well-established risk factor for onset and unfavourable course of depression. The best established dimensional measure of personality as a risk factor for depression is the construct of Neuroticism. Neuroticism is one of the five major dimensions of personality (Five Factor Model; FFM; Costa and McCrae, 1992). This trait reflects the disposition to experience negative affect, including anger, anxiety, irritability, emotional instability, low mood, and self-consciousness [63]. Persons with high levels of neuroticism respond poorly to psychosocial stress, interpret ordinary situations as threatening, and they can experience minor frustrations overwhelmingly as hopeless. A substantial body of research to support its heritability, childhood antecedents, temporal stability across the life span, and universal presence [64, 65].

Other personality psychopathology constructs have been established as well, such as the tendency to be paranoid, avoidant or dissocial behavior [for example measured with the Dimensional Assessment of Dimensional Psychopathology Self-Report; DAPP-SF; 66]. Personality pathology has been strongly linked to psychiatric disorders, such as depressive and anxiety disorders [67-69]. The risk of comorbid personality disorders for major depressive disorder has been estimated at 45% [70], and ranges from 35% to 52% for anxiety disorders. High personality pathology, increases the risk of depression, its unfavourable course, and a higher relapse rate [42, 43, 68, 71]. However, the effects of personality pathology on treatment outcome may be substantially lower when taking baseline symptom level into account, usually interpreted as severity. Surprisingly, the likely intermediary effects (either as a mediator variables, or a moderator variables) of baseline depression severity on the relationship between personality pathology and treatment outcome have received little attention in the current literature [72-74].

Given the heterogeneous nature of depression, focusing on individual symptoms may yield novel insights into the relationship with personality traits, and the course of depression [42-44]. Although one study has demonstrated that neuroticism was related to all nine depression symptoms [51], another found specific associations with appetite/weight and sleeping

problems [75]. Assessing the link between personality and individual symptoms might increase our ability to target (psychotherapeutic) treatment strategies earlier and, more specifically, on certain symptom patterns.

1.4.3 Somatic factors: low-grade inflammation and mood states

Most somatic diseases or infections cause physical symptoms, but also mental- and behavioural changes. These behavioural changes are defined as "*sickness behaviour*". Sickness behaviour is generally regarded as an organized group of reward-oriented behavioural and motivational changes that accompany inflammation and infections [76-79]. Sickness behavior symptoms show considerable overlap with depressive symptoms (e.g., anhedonia, anorexia, low concentration, low energy, low libido, psychomotor slowness, and irritability). Therefore, researchers have hypothesized that depression is a maladaptive or exacerbated form of sickness behavior in some patients with chronic low-grade inflammation [76-78, 80-82]. Besides their reward-sensitivity related symptoms, recent studies suggest that also trauma- and anxiety-related symptoms are related to inflammatory markers, resulting in a mix of overlapping symptoms of mood, anxiety, and post-traumatic stress disorder [83-86]. Researchers have theorized that sickness behaviour holds some evolutionary advantages and has protective mechanisms for the individual, because it preserves energy resources needed for healing infection or other diseases and it may help prevent the transmission of its potential infectious agent [78, 79]. During an inflammatory response, the innate and adaptive immune systems are activated and pro-inflammatory cytokines are produced. The causal chain may involve somatic triggers inducing an inflammatory response, followed by sickness behavior. Sickness behavior in turn overlaps with- and induces depression, with additional positive feedback loops between (neuro) inflammation and (neuro) degenerative processes [78, 79, 82]. Evidence from meta-analyzes suggests that depressed patients have higher circulating concentrations of acute-phase proteins and pro-inflammatory cytokines compared to healthy subjects [87-92]. Also inflammatory markers after *ex vivo* induction of lipopolysaccharide (the cell membrane of Gram-negative bacteria), demonstrated significant associations with depression. However, other studies in this context have not found significant associations [91, 92]. A causal pathway in which inflammation causes symptoms of anxiety has been less established [93-95].

Inflammatory markers and depression have been linked, but effect sizes were generally small with limited clinical relevance for the individual patient [79, 96]. Low-grade inflammation may only be strongly linked to a subset of depressive symptoms that overlap with sickness behaviour [97, 98], and therefore may only be involved in the pathogenesis of a subset of depressed patients. The effect size between inflammation and individual symptoms may be higher than depression as a syndrome. Identifying associations between pro-inflammatory markers and specific depressive symptoms could be important for the advance of personalized medicine [96]. Nevertheless, few clinical studies have analyzed whether inflammatory markers are associated with specific depressive symptoms [96, 97, 99, 100]. Moreover, prospective studies regarding anxiety symptom severity remain scarce.

1.4.4 Methods: improving accuracy with innovative statistical methods

One way to increase the predictive value of these variables may be to use multivariate statistical models. Most clinical data thus far have been analyzed by using data modelling methods (such as regression analysis) and selecting only a collection of selected predictors. It is possible that more complex (including nonlinear and higher dimensional) patterns exist in the data, which can efficiently be detected when analyzing all available data simultaneously using machine learning approaches [101, 102]. These approaches are able to examine huge numbers of potential predictors, such as current individual symptoms, in an unbiased manner while preventing overfitting [103]. Machine learning may be more time efficient, better suited for large and complex datasets, and better able to detect complex patterns in the data than current data-modelling [104]. These advanced methods may be better suited to handle depression heterogeneity. Moreover, machine learning incorporates less human decision making than traditional methods, and could be suited for full automatization [104-106].

Over the past decade more modern techniques of machine learning have also been applied in the field of psychiatry. Thus far, machine learning studies in the field of psychiatry have been promising. A recent meta-analysis, which included 20 studies that predicted the therapeutic outcome of depression using machine learning algorithms, found an overall accuracy of .82 (95% confidence interval [CI] .77–.87; Lee et al., 2018). However, recently published papers have demonstrated only limited added value of machine learning over traditional regression analyzes [107, 108]. Additionally, other studies found that when predicting suicide, machine learning did not outperform regression analysis and resulted in

positive predictive values below 0.01, thus limiting the practical utility of these predictions [109, 110]. Despite the increasing number of publications in this field, machine learning has yet to move towards clinical application [111].

1.5 Aim, research questions and hypothesis of this dissertation

The present dissertation aims to expand our knowledge of depression by researching the symptom-specific longitudinal characteristics, risk-factors, and methods of analyzing depression severity in which individual symptoms are taken into account. This dissertation will mainly focus on depression, although anxiety has been studied as well, as anxiety is highly prevalent in patients with depression and share a common etiology. This brings us to the following research questions:

Main research question:

Can major depressive disorder be characterized as a unified syndrome?

This can be divided in the following sub-questions and hypotheses:

1. Is the course of individual depressive symptoms uniform over time?

We hypothesized that depression is a disorder with substantial within-person heterogeneity between symptoms in terms of intercepts, slopes, and variability.

2. Are individual symptoms of depression related to the same risk factors?

We hypothesized that risk factors are associated with the course of specific symptoms, rather than depression as a homogeneous construct, with similar associations for each symptom. We hypothesized that low-grade inflammation inflammatory markers demonstrate the strongest associations with symptoms that overlap with sickness behaviour.

3. Are advanced statistical methods more adequate to handle depression heterogeneity?

We hypothesized that machine learning techniques are better in detecting complex patterns in the data and would outdo traditional regression analysis techniques and achieve higher levels of accuracy when predicting the course and onset of depression and anxiety. Moreover, we hypothesized that machine learning would be particularly effective when symptom-specific features of current depression and anxiety are included to predict future disorders.

1.6 Cohorts used in this dissertation

This thesis is built on pre-existing data from the Netherlands Study of Depression and Anxiety (NESDA; Chapters 2, 3, 5, 6, 7) and the Leiden Routine Outcome Monitoring Study (ROM; Chapters 4).

NESDA is an ongoing multi-site naturalistic longitudinal cohort study, which aims to investigate the course and consequences of depressive and anxiety disorders. The first wave (baseline) lasted from 2004 to 2007, and the sixth wave of measurement at the 9-year follow up finished in 2016. NESDA is a cohort study that recruited from the community (*n* = 564; 18.9%), general practice (*n* = 1,610; 54.0%), and secondary mental healthcare [n=807; 27.1%; 112]. It includes patients with a current or lifetime depressive or anxiety disorder as well as healthy controls. By applying only few exclusion criteria, NESDA aimed for a cohort that is representative for diverse populations of healthy controls and patients with depression and anxiety [112].

The Leiden Routine Outcome Monitoring Study (ROM) is an ongoing prospective cohort study of the Leiden University Medical Center (Department of Psychiatry, in cooperation with mental health care provider GGZ Rivierduinen) which was carried out to assess treatment progress/outcome for patients with mood, anxiety, and/or somatoform disorders in a naturalistic setting [113]. The first assessment occurred during an intake procedure; research nurses interviewed patients using the Mini International Neuropsychiatric Interview-Plus [MINI-Plus; 114]. Additionally, patients completed a number of self-report questionnaires which were repeated during treatment. ROM data are collected systematically to assess treatment effectiveness in everyday clinical practice, to inform clinicians and patients about treatment progress (Carlier et al., 2012b; Lambert, 2017; Lambert et al., 2018).

1.7 Dissertation outline

In **chapter 2**, we assessed the longitudinal symptom-specific course trajectories and within-person variability of major depressive disorder over a 9-year period (NESDA data). More specifically, we aimed to answer which symptoms have clinically favourable characteristics and which show a more persistent course. We addressed some of the methodological gaps in earlier studies, by assessment of within-person variability over time, in which repeated measures are nested within persons.

In **chapter 3**, we examined whether preceding chronic depression, defined as being depressed for at least 2 years (during a patient's past 4 years before baseline) and level of neuroticism could predict the 9-year trajectory of individual depressive symptoms (NESDA data). In particular, the focus was on the symptom-specific differences.

In **chapter 4**, the prognostic value of a broad range of dimensional personality pathology on treatment outcome among patients with depression and/or anxiety disorders is investigated (ROM data). We hereby assessed the potential mediating and/or moderating effects of baseline symptom level.

In **chapter 5,** we examined the associations between basal levels and LPS-induced inflammatory markers and individual depressive symptoms over the course of 9 years. Inflammation has been repeatedly linked to depression, presumably as a consequence of sickness-behavior. However, not all depression symptoms may be related to sickness behavior equally.

In **chapter 6**, we extended our research on inflammation by also examining whether basal as well as LPS-induced inflammatory markers determined at baseline are associated with the course of domains of anxiety symptomatology.

Chapter 7 has a more methodological approach. In this chapter, we assessed whether using more complex statistical methods would be better suited for dealing with the complexity of depression heterogeneity. We compared the performance of three methods: traditional multinominal logistic regression, a basic probabilistic machine learning algorithm (naïve Bayesian classifier [115], and a more advanced automated machine learning method (Auto-sklearn [106]) to predict DSM-IV-TR psychiatric diagnoses at 2-, 4-, 6-, and 9-year follow up with different sets of predictors, including current individual symptoms.

Finally, in **chapter 8**, we summarized the general conclusions of this dissertation and discuss the strengths and limitations of our studies. In addition, we discuss the clinical implications derived from our studies and recommendations for further research.

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