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*Review*

# CHRONOBIOLOGICAL PREDICTORS OF DEPRESSION RELAPSE: FOR PROGNOSTIC MODEL DEVELOPMENT - A SYSTEMATIC REVIEW

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## SUMMARY

***Background:*** *Depressive disorders are characterized by fluctuating symptom severity, and developing an individual prognostic model for relapse is crucial for effective prevention. Chronobiological factors are poorly understood in this context.*

***Methods:*** *A systematic search was conducted to identify articles related to the prognosis of depression recurrence based on chronobiological factors. Relevant clinical studies were included, while reviews and case reports were excluded. A total of 14 articles were selected for review.*

***Results:*** *The included articles focused on various chronobiological factors, including circadian biorhythms, individual chronotype, mood swings, seasonal patterns, diurnal cortisol fluctuations, and light therapy. The accuracy of personified prognosis ranged from 22.7% to 93.8%, and the prognostic value of specific predictors in group prognosis varied from 23.9% to 54%. Methodological differences and limitations hindered direct comparison and clinical applicability.*

***Conclusions:*** *Developing precise and practical models for depression recurrence prognosis remains limited. Parameters of circadian rhythm showed the highest accuracy for short-term prognosis, and the use of digital technologies, including AI, enhanced prognostic value. Relapse seasonality had limited practical applicability. Integrating other chronobiological factors into prognostic models requires further research. Utilizing digital technologies, including AI, can improve the accuracy and range of personified prognosis. Only a few selected parameters of the human chronobiological system were considered in the examined studies. There are indications of the other chronobiological factors that could be included in the integrated prognostic model of recurrence for its further improvement.*

***Key words:*** *chronobiology - depression - depressive disorder - prediction - prognostic model – relapse*

***Abbreviations:*** *AI – artificial intelligence; BD, BD-I, BD-II – bipolar disorder, type 1 and 2; BLT – bright white light therapy; CT – controlled trial; CAR – cortisol awakening response; DE – depressive episode; DST – dexamethasone suppression test; DRL – dim red light therapy; ECT – electro-convulsive therapy; HR – heart rate HME – hypomanic episode; HPA – hypothalamic pituitary adrenal axis; LT – light therapy; MDD – major depressive disorder; MDE – major depressive episode; ME – manic episode; MEQ – morningness-eveningness questionnaire; RCT – randomized controlled trial; SADS-L – schedule for Affective Disorders and Schizophrenia Lifetime Version; SAD – seasonal affective disorder; SPAQ – seasonal Pattern Assessment Questionnaire; SSQ – seasonal Screening Questionnaire; CRM – smartphone app Circadian Rhythm for Mood; SCID-NP – structured Clinical Interview for DSM-III-R (non-patient edition); TSH – thyroid-stimulating hormone; TRH – thyrotropin-releasing hormone*

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## INTRODUCTION

The Global Consortium for Depression Prevention concluded that our best chance to combat the global burden of depression is to provide preventive intervention to people at risk (Leerssen et al. 2020, Whooley 2012). Possibility of prophylactic treatment in patients already diagnosed with recurrent and chronic affective disorders and also prevention of manifestation of such disorders should, in ideal scenario, be based on developing prognostic model of the disorder course that will show periods of maximum risk of exacerbations. Prognostic can be both personified or built for certain clinical group. Despite the large amount of prognostic factors of different nature (genetic, biochemical, psychosocial, personal, etc.) and studies about prognosis of depressions, the task of developing chronological prognostic model of relapse based on available verifiable factors remains far from solved (Moriarty et al. 2021). In this regard, factors of chronobiological nature remain poorly understood and underappreciated.

The aim of our review was to describe as complete as possible list of chronobiological predictors of manifest, worsening and relapse of depressions studied in terms of prognostic relapse and recurrence modeling.

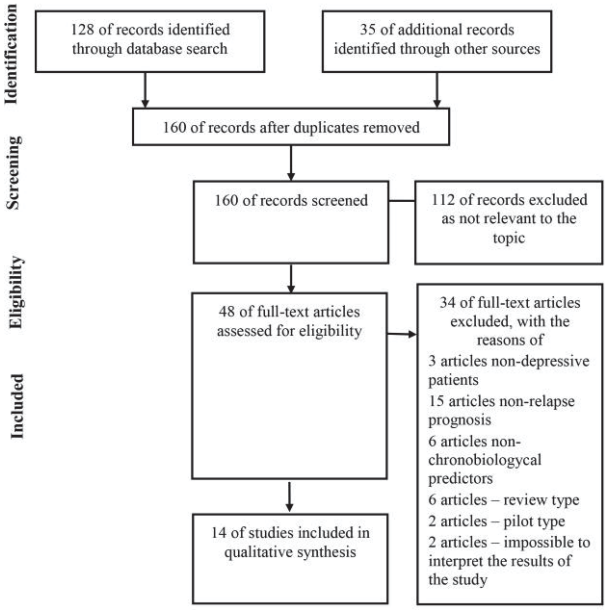
In its mainstream interpretation, chronobiological factor as subject of chronobiology study is any parameter of time organization of biological system, more often – rhythmic manifestation of any process in system, usually conjugated with certain 'ecological' rhythms (circadian, circaseptan, circalunar, seasonal, circannual, etc.). Any vital sign can potentially be a chronobiological factor, including therapeutic or other environmental effect if they are considered in the aspect of their organization in time and if there are also signs of rhythmicity of these processes and signs (Katenis et

al. 2015). In accordance with such broad understanding, potential number of chronobiological parameters is incalculable. However, real amount of biorhythms and factors affecting them in scientific research of mental disorders is significantly lower. Researchers focus on quite calculable amount of indicators that demonstrated their potential or confirmed clinical significance and applicability. First of all they include indicators of circadian and seasonal periodicity. However, we can't deny the possibility of new, as yet unknown chronobiological parameters appearing.

In our review we didn't conducted quantitative meta-analysis of existing studies on chronobiological predictors of relapse due to significant differences between them. The differences concern certain studied factors, studies design, methodological approaches and certain methods, timings and means of developing prognostic model and other details of studies.

## METHODS

Systematic search was conducted in PubMed, Web of Science, Cochrane, e-Library up to 31 March 2023. The stages of selecting articles for systematic review are shown in Figure 1. PRISMA method (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) was used to find all published works related to prognosis of depression relapse based on chronobiological factors. Articles related to chronobiological predictors, prognosis of relapses, prognostic models of depression course were identified using predefined search terms. Search query included ((chronobiology OR biorhythms) AND (relapse OR manifestation OR aggravation) AND (prognosis OR predictor OR prediction) AND depression) OR (biorhythms AND "predicting relapse of depressive disorder") OR (chronobiology AND prognosis AND depression). The PICOS (Population Intervention Comparison Outcome Settings) in our review was as follows: P – patients with recurrent depression or persons with potential risk of depression manifesting, I – chronotherapeutic intervention (if applicable), C – clinical, clinical-dynamic, chronotypological, chronotherapeutic control groups, O – manifest, worsening, relapse of depression, S – in a setting of RCT, prospective observational studies or case-control studies. Planned studies (protocols) and clinical case reports were excluded. Systematic reviews and meta-analyses strictly related to the aim of our review were not found as result of our search, however, some reviews elaborated on important nuances as their additional task, which is used in discussion of the results. In the main analysis were also included original studies with indirect relevance to the aim of our review, without development of prognostic model of relapses but when discussed by at least two authors labeled as being within the field of chosen subject: (1) Chronobiological predictors of depression course associated with the use of chronotherapy (light therapy), (2) Individual chronotype of patients as predictor of affective disorder course. There were no restrictions by year of publication. Only articles in English were selected for main analysis (Figure 1).




PubMed search algorithm is as following ((chronobiology OR biorhythms) AND (relapse OR manifestation OR aggravation) AND (prognosis OR predictor OR prediction) AND depression) OR (biorhythms AND "predicting relapse of depressive disorder") OR (chronobiology AND prognosis AND depression)

**Figure 1.** PRISMA flow diagram of the literature search algorithm on the topic of the chronobiologycal predictors of depressive relapse

## RESULTS

### Research design

Examined studies didn't have unified methodology. Design of all examined works were unified by presence of prospective observation period of research group members during which hypothesis of the study was tested and prognostic model was validated where it was built based on initial data (Table 1). The duration of prospective observation in this case varied between 20 days and 10.4 years. In 6 works observation period was 12 months or shorter, in 6 studies – 4 years or longer. The choice of observation duration was mainly associated with the nature of prognostic factor and parameter of projected clinical event. So, in 3 studies of modeling mood changes based on circadian rhythm observational period was minimal – less than 2 years, in all 3 studies of seasonal depression pattern stability observational period was maximal – from 5-8 to 10.4 years. In studies devo0ted to predicting depression manifest or relapse based on single or short-term data collection (for example, such as cortisol level) this period was intermediate term – 4 years (in 2 out of 3 studies). Minimal observation period was featured by works that studied short mood swings during relapse ('mini-cycles' – from 20 days of observation)

**Table 1.** Original studies of chronobiological predictors of depressions relapse

| Authors, year of publication | Chronobiological predictor | Prospective observation period, personification / prognosis for a group | Projected parameters of relapse | Modeling technology | Main group (number of patients) | Study type / control group | Key results and conclusions | Practical validity or other practical value |
|---|---|---|---|---|---|---|---|---|
| Cho Ch.-H. et al. 2019 | Evaluation of activity, sleep, light exposure and heart rate (in all 130 signs of circadian rhythm) | 2 years Personified prognosis | Mood state for the next 3 days, the absence of episode or the onset of DE, ME or HME | Digital data collection via wearable devices and apps, clinical assessment, prediction algorithm, developed with the help of machine learning | 55 patients with BD, BD-I and BD-II | Comparative study, clinical subgroups comparisons | Prognosis accuracy in all patients, patients with MDD, patients with BD-I and patients with BD-II was 65%, 65%, 64% and 65% respectively. Prognosis accuracy for the absence, DE, ME and HME 85.3%, 87%, 94% и 91.2%. | Perspective application in real clinical practice |
| Cho Ch.-H. et al. 2020 | Four H-indicators for HR, activity, sleep and light exposure, selected according to the results of preliminary studies (Cho Ch-H et al. 2019) | 12 months Personified prognosis | Mood state for the next 3 days, the absence of episode or the onset of DE, ME or HME | App Circadian Rhythm for Mood (CRM) that uses data of wearable activity tracker. Report on prediction trends with behavioral recommendations | 10 patients in CRM group | CT: 33 patients without CRM in control group | In the CRM group there were 96.7% fewer DE, 96.1% fewer ME, than without CRM. In CRM group there were positive changes in behavior regarding health thanks to warnings | App was effective for preventing relapses, improvement of prognosis and encouraging better behavior in regards to health |
| Lee H.-J. et al. 2022 | Illumination, step, HR and sleep data | On average 279.7 days for patient (72-1515 days range) Personified prognosis | Episode prediction model takes into account three types of mood episodes: MDE, ME and HME. | App «eMoodChart», wearable tracker Fitbit Charge HR, independent clinical assessment once every 3 months. Minute-by-minute data with a patented algorithm Fitbit | 495 patients with MDD, BD-I and BD-II, 270 affective episodes in 135 subjects | Case-control study with independent clinical assessment of effectiveness of prognostic model | Key predictors of MDE and HME were sleep- and HR-related peculiarities. Step counting contributed to the model of ME prognosis. Certain predictors of MDE, ME and HME were thoroughly described. | Accuracy of prognosis of any type of episode for the next 3 days for all participants and patients with MDD, BD-I and BDII was 91.9, 93.8, 93.7 and 92.4% respectively. |
| Novak D. et al. 2014 | Interdiurnal stability of circadian rhythm based on actigraphy and mood self-assessment | 7 years Personified prognosis | Depression or mania relapse | Actigraphy (Actiwatch device (Camntech, Cambridge)) and questionnaire | 8 patients with BD | Case-control study | Analysis of interdiurnal actigraphy and mood self-assessment stability was proposed. Sensitivity 65% and specificity 68%. | Planned prospective study based on developed system |

*Notes:* DE - depressive episode; ME - manic episode; HME - hypomanic episode; MDD - major depressive disorder; MDE - major depressive episode; SAD - seasonal affective disorder; BD - bipolar disorder; BD-I and BD-II - types 1 and 2: CRM - smartphone app Circadian Rhythm for Mood; HR - heart rate; CAR - cortisol awakening response; DST - dexamethasone suppression test; HPA - hypothalamic pituitary adrenal axis; TSH - thyroid-stimulating hormone; ECT - electro-convulsive therapy; TRH - thyrotropin-releasing hormone; SADS-L - Schedule for Affective Disorders and Schizophrenia Lifetime Version; SPAQ - Seasonal Pattern Assessment Questionnaire; SSQ - Seasonal Screening Questionnaire; SCID-NP - Structured Clinical Interview for DSM-III-R (non-patient edition); RCT - randomized controlled trial; CT - controlled trial; MEQ - Morningness-eveningness questionnaire

**Table 1.** Continues

| Authors, year of publication | Chronobiological predictor | Prospective observation period, personification / prognosis for a group | Projected parameters of relapse | Modeling technology | Main group (number of patients) | Study type / control group | Key results and conclusions | Practical validity or other practical value |
|---|---|---|---|---|---|---|---|---|
| Melo M. C. et al. 2019 | Individual chronotype and prognostic factors of MDD (anxiety, functioning, affective episodes and hospitalisations) | 18 months Group prognosis | BD course prognosis | Demographic questionnaire and clinical scales for rating anxiety, functioning and chronotype with subsequent monthly clinical assessment | 80 patients with euthymic BD | Comparative study, subgroup comparisons based on individual chronotype | Evening chronotype with BD indicates a poor prognosis because of its association with anxiety, decreased performance and the large number of affective episodes | Relevance of further study and prophylactic correction of circadian rhythm disorders in patients with BD even during euthymia |
| Chan J. et al. 2023 | Evening chronotype in patients with depression, chronotherapy | 5 months Group prognosis | Remission prognosis in connection with change in circadian preferences after 5-week chronotherapy | Secondary analysis of data, collected in RCT of light therapy for non-seasonal depression and associated evening type. MEQ. Models of generalized estimation equations. | 91 adult patient with non-seasonal unipolar depression and evening chronotype | RCT with the randomization on 1) bright light therapy (BLT group) or 2) dim red light therapy (DRL group) | 33 participants (36%) experienced a change of evening chronotype on the 5-th week, which predicted 2.6-fold remission increase during 5-month observation. | Further factor analysis may be useful for determining whether certain elements in MEQ are influencing the change in circadian preferences in future study with larger sample size |
| Benedetti F. et al. 1996 | 'Mini-cycles' of mood fluctuations in patients at the time of relapse | Period of inpatient treatment from 20 days Personified prognosis | Fluctuations of symptoms severity of affective relapse | Mood was evaluated by patients via visual analogue scale three times a day | 22 inpatients (13 with MDD and 9 with BD) | Case-control study | 22.7 % of patients demonstrate predictable cyclic patterns, with duration from 6 to 14 days. | Cyclic mood fluctuations influence the process of making clinical decisions (change of treatment) and DE outcome. |
| Thompson C. et al. 1995 | Seasonal pattern of depression in accordance to DSM-III-R criteria and predictors of subsequent seasonality | From 5 to 8 years Group prognosis | Preservation of the seasonal pattern of relapses | Study included SADS-L, SPAQ, SSQ and SCID-NP | 93 individuals diagnosed with accordance to DSM-III-R criteria of recurrent major depressive disorder of a seasonal nature | Comparative study, subgroups with seasonal, non-seasonal and remission course | 38% retained seasonal pattern. Predicted future seasonality: duration of DE, frequent relapses, cyclothymic personality. | Definition of SAD DSM-III was too broad. DSM-IV has expanded it even more, and it has been suggested to reverse that change |

*Notes:* DE - depressive episode; ME - manic episode; HME - hypomanic episode; MDD - major depressive disorder; MDE - major depressive episode; SAD - seasonal affective disorder; BD - bipolar disorder; BD-I and BD-II - types 1 and 2: CRM - smartphone app Circadian Rhythm for Mood; HR - heart rate; CAR - cortisol awakening response; DST - dexamethasone suppression test; HPA - hypothalamic pituitary adrenal axis; TSH - thyroid-stimulating hormone; ECT - electro-convulsive therapy; TRH - thyrotropin-releasing hormone; SADS-L - Schedule for Affective Disorders and Schizophrenia Lifetime Version; SPAQ - Seasonal Pattern Assessment Questionnaire; SSQ - Seasonal Screening Questionnaire; SCID-NP - Structured Clinical Interview for DSM-III-R (non-patient edition); RCT - randomized controlled trial; CT - controlled trial; MEQ - Morningness-eveningness questionnaire

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|---|---|---|---|---|---|---|---|---|
| Sakamoto K. et al. 1995 | Seasonal pattern of depression in accordance to DSM-III-R criteria and predictors of subsequent seasonality | 10.4 years Group prognosis | Long-term stability of seasonal pattern | SADS-L and Hamilton Depression Rating Scale, SAD version, to get information about disease course and its symptoms, especially about atypical vegetative symptomatology | 41 individuals with two consecutive episodes of seasonal depression | Comparative study, 5 groups comparisons based on degree of loss of seasonality and other peculiarities of relapses of seasonal nature | As a result only 12 met all of DSM-III-R criteria for SAD. All 41 patients had at least one seasonal episode. Manifestation of atypical vegetative symptoms during earlier episodes predicts subsequent seasonality. | Diagnostic criteria of SAD – screening criteria. 40% of patients with initial diagnosis of SAD will have pronounced seasonality in the future. DSM-III-R criteria modification in regard to 60-day windows and number of seasonal episodes may be preferable. |
| Schwartz P. J. et al. 1996 | Winter pattern of seasonal depression | 8.8 years Group prognosis | Stability of seasonal pattern and its connection with light therapy and antidepressant treatment, the peculiarities of the course (bipolar, unipolar) | The 'life chart' of entries for variables (life events, medications/treatment, lightbox use, and mood) on a monthly basis. Semi-structured interview. Predictors assessment via regression analysis. | 59 patients with winter SAD | Comparative study with clinical groups comparisons | 25 patients (42%) retained winter seasonality. Varying degrees of non-seasonal depression in 26 (44%). Remission in 8 (14%). Division into unipolar and bipolar subgroups wasn't useful | Long-term persistence of winter depression in the majority of initial patients with SAD insures prognostic effect and validity of Rosenthal criteria for winter SAD |
| Cosgriff J. P. et al. 1990 | High cortisol level in patients with clinical recovery after ECT | 6 months Group prognosis | The onset of relapse during prospective observation period | Mean value of daytime cortisol level was calculated by averaging nine values. TSH delta level as the difference between baseline TSH level and peak TSH level after stimulation through TRH | 17 patients that met the criteria of recovery between 3 and 10 days after completion of ECT. | Comparative study, subgroups comparisons of patients with and without relapse. | Patients with relapse during 3 months had elevated cortisol level. Cortisol levels higher than average were largely prognostically valuable in the sample as a whole. | To consider possibility of assessment of cortisol level during second half of the day only in difficult inpatients, method may not apply in outpatients |

*Notes:* DE - depressive episode; ME - manic episode; HME - hypomanic episode; MDD - major depressive disorder; MDE - major depressive episode; SAD - seasonal affective disorder; BD - bipolar disorder; BD-I and BD-II - types 1 and 2: CRM - smartphone app Circadian Rhythm for Mood; HR - heart rate; CAR - cortisol awakening response; DST - dexamethasone suppression test; HPA - hypothalamic pituitary adrenal axis; TSH - thyroid-stimulating hormone; ECT - electro-convulsive therapy; TRH - thyrotropin-releasing hormone; SADS-L - Schedule for Affective Disorders and Schizophrenia Lifetime Version; SPAQ - Seasonal Pattern Assessment Questionnaire; SSQ - Seasonal Screening Questionnaire; SCID-NP - Structured Clinical Interview for DSM-III-R (non-patient edition); RCT - randomized controlled trial; CT - controlled trial; MEQ - Morningness-eveningness questionnaire

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|---|---|---|---|---|---|---|---|---|
| Vrshek-Schallhorn S. et al. 2013 | CAR | 4 years Group prognosis | Manifest and repeated attacks of MDE | Structured clinical interview for DSM-IV, questionnaire and 3-days protocol which measures CAR and circadian rhythm (six times a day). Up to four subsequent yearly interviews. | 270 older adolescents (75 boys and 195 girls; median age is 17.06 years when measuring cortisol level) | Correlational study | CAR – important predictor of MDE. Prognostic power of CAR deteriorated by 3% per month. CAR predicts initial and repeated attacks, but relapses – with greater strength, marginally predicts relapse for a time span greater than 36 months | Current data doesn't reveal anything about biological mechanism that connects CAR with the risk of MDE |
| Hardeveld F. et al. 2014 | CAR, DST and evening cortisol level, and also interaction of HPA axis parameters with childhood trauma and life events | 4 years Group prognosis | The presence of relapse of MDD 1 month, 6 months, 1 year and 2 years after initial assessment | Seven cortisol spit samples at baseline. Diagnostic interview twice the 4 years. Cox regression analysis with adjustment for covariates | 549 individuals diagnosed with MDR in remission during six months preceding the initial assessment. | Correlational study | 131 patients (23.9%) had relapse of MDD during 2 years, 193 (35.2%) during 4 years. Median time before relapse 27.4 months. High CAR – indicator of relapse 'sign', low CAR – indicator of 'scar' of current depression. Total daily cortisol wasn't associated with relapse. | CAR isn't used as diagnostic instrument in clinical setting, it is a valuable instrument in studies. Analysis hasn't confirmed the assumption that higher CAR is an indicator of hypersensitivity towards psychosocial stress |
| Meesters Y. et al. 1993 | Light therapy | 26 days of the experiment (base period) during remaining part of winter up to 15 April (observation period) Group prognosis | The onset of relapse and the duration of remission | Diurnal mood fluctuations based on daily morning and evening self-assessments, weekly assessments via depression scales | 30 outpatients with depression | RCT with the randomization of morning and evening chronotherapy subgroups | Frequency of consecutive relapses of depression during remaining part of winter after treatment – 54%. | Relapse can be prevented during remaining winter season, if the treatment is done in the very first stage of depression manifestation |

*Notes:* DE - depressive episode; ME - manic episode; HME - hypomanic episode; MDD - major depressive disorder; MDE - major depressive episode; SAD - seasonal affective disorder; BD - bipolar disorder; BD-I and BD-II - types 1 and 2: CRM - smartphone app Circadian Rhythm for Mood; HR - heart rate; CAR - cortisol awakening response; DST - dexamethasone suppression test; HPA - hypothalamic pituitary adrenal axis; TSH - thyroid-stimulating hormone; ECT - electro-convulsive therapy; TRH - thyrotropin-releasing hormone; SADS-L - Schedule for Affective Disorders and Schizophrenia Lifetime Version; SPAQ - Seasonal Pattern Assessment Questionnaire; SSQ - Seasonal Screening Questionnaire; SCID-NP - Structured Clinical Interview for DSM-III-R (non-patient edition); RCT - randomized controlled trial; CT - controlled trial; MEQ - Morningness-eveningness questionnaire

and prognostic value of individual chronotype (5 and 18 months of observation) and also such therapy methods as light therapy and ECT (from around 4 months of winter season to 6 months after ECT).

From the point of randomization and control group presence studies also significantly differed. In 3 works, including studies on depression manifest in healthy at the time of data collection adolescents, randomization wasn't conducted and there was no control group. In another 2 studies on relapse prediction 'internal' clinical control of projected affective episodes was used. Out of the remaining 9 of examined works the largest part was comprised of studies that were divided into comparison subgroups inside experimental group by parameters of clinical signs, peculiarities of affective disorder course (6 studies total). Randomization predictably was carried out in 2 studies, devoted to prognostic value of light therapy, including at the same time the role of patients individual chronotype. Control group also initially was envisaged in 1 work that studied validity of prognosis and prevention of relapse using digital devices with feedback with patients. Overall ratio of non-randomized non-experimental studies (comparative, correlational or case-control) to controlled trials (CT) and RCT in the studied sample was 11:3. In 9 studies prognosis was made for clinical group, in 5 – personified prognosis of mood fluctuations or risk of relapse of ME, DE or HME (Table 1).

## Patients selection

Total number of patients in 13 selected articles was 1550 individuals in the main research groups, in another 1 study devoted to predictors of depression manifest 270 healthy young people were studied (median age at the start of study – 17 years). Clinical groups of patients: major depressive disorder (MDD) and bipolar disorder type 1 and 2 (BD-I and BD-II), major depressive episode (MDE), seasonal affective disorder (SAD), non-seasonal unipolar depression. In different studies due to large variability in publication year classifiers DSM-III-R or DSM-IV were used.

## Chronobiological predictors

4 articles (2 of them share an authorship Cho et al. (2019, 2020) were devoted to prognostic evaluation of circadian biorhythms (physical activity, sleep, illumination, HR, mood self-assessment), 2 – to circadian preferences (individual chronotype) of the patient, including due to conducted light therapy, 1 – to evaluation of 'minicycles' of mood swings (duration up to a few days) during depression relapse on inpatient level, 3 – to seasonal pattern of relapses and predictors of subsequent seasonality of manifest episodes, 3 – to prognostic value of diurnal cortisol fluctuations (CAR, DST and evening cortisol level) and 1 – to light therapy of SAD as the factor, modifying recurrence in the coming season after its use.

## Circadian factors

Only a few selected parameters of the human circadian system were considered in the examined studies. Novak et al. (2014) conducted a study on the inter-diurnal stability of circadian rhythm using actigraphy and mood self-assessment. Although the study provided key ideas for analysis and had a long prospective observation period of 7 years, the limited number of subjects (8 individuals) and lack of statistical reliability posed significant limitations. The study achieved a sensitivity of 65% and specificity of 68% for the prognosis of affective episodes.

Cho et al. (2019, 2020) examined 130 indicators of circadian rhythmicity and identified 4 specific indicators (H-indicators) for heart rate, activity, sleep, and light exposure using mathematical analysis and machine learning algorithms. These indicators were acquired through wearable devices, and the authors used them to develop a CRM app that provided mood trends and behavioral recommendations. Lee et al. (2022) also utilized digital technologies and similar circadian indicators, incorporating subjective mood assessment and data from wearable devices. The practical application of these algorithms showed high accuracy in predicting the onset of episodes, happening during the next 3 days, in individuals with bipolar disorder (BD), ranging from 64% to 93.8%, and high effectiveness in preventing predicted relaps, ranging from 96.7% to 99.5%.

Another aspect of circadian predictors is the patient's circadian preferences or chronotype. Melo et al. (2019) studied the association between chronotype and other prognostic factors of BD. Evening chronotype was found to be associated with an unfavorable prognosis due to its correlation with other predictors. Chan et al. (2022) conducted a randomized controlled trial on patients with non-seasonal depression and evening chronotype, comparing the effects of bright light therapy and dim red light therapy. The change in chronotype during the study predicted a 2.6-fold increase in remission rate. Further factor analysis in future study with larger sample size, in authors' opinion, may be useful to determine whether the certain elements in MEQ are influencing the change in circadian preferences.

## Infradian (multi-day) factors

This group of predictors is represented by a single, relatively old study by Benedetti et al. (1996). The study examined fluctuations in symptom severity during depressive relapse using self-assessment via a visual analogue scale three times a day (8:00 a.m., 3:00 p.m., and 10:00 p.m.) in inpatients with major depressive disorder (MDD) and bipolar disorder (BD) throughout their inpatient treatment period. Despite the small sample size, the study concluded that 22.7% of patients exhibited predictable cyclic patterns in their subjective state, lasting from 6 to 14 days. These cyclic mood

fluctuations have implications for clinical decision-making, including treatment adjustments and the outcome of depressive episodes, highlighting the importance of studying and considering these fluctuations in clinical practice.

### Seasonal pattern

Prognostic value of seasonality based on the reviewed articles following the description of seasonal affective disorder (SAD) criteria by Rosenthal et al. (1984) in DSM-III-R and DSM-IV generated significant interest. The validity of screening scales for diagnosing SAD, such as the Seasonal Pattern Assessment Questionnaire (SPAQ) and Seasonal Screening Questionnaire (SSQ), was actively discussed. Three articles from 1995-1996 included in the review (Sakamoto et al. 1995, Schwartz et al. 1996, Thompson et al. 1995) reached similar conclusions. Approximately 29.3% to 42% of patients diagnosed with SAD exhibited a retained seasonal pattern in the future. Additional predictors of seasonality described in these studies were discussed in general terms, making evaluation difficult. Factors such as long depressive episodes, high frequency of relapses, and cyclothymic personality were identified as potential predictors of future seasonality. However, other examined factors, including treatment history, daily mood fluctuations, number of previous episodes, and family history of depression, did not predict the seasonal course of the disease. Sakamoto et al. (1995) found that the manifestation of atypical vegetative symptoms during earlier seasonal depressive episodes could predict subsequent seasonality, and the use of antidepressants might be associated with a change from seasonal to non-seasonal patterns in some cases. Schwartz et al. (1996) suggested that dividing the study group into unipolar and bipolar subgroups was not useful for identifying recurrence differences. Overall, the authors agreed on the validity of SAD criteria, the usefulness of scales for evaluation, and the prognostic value of seasonality patterns, with some modifications, as clinical and prognostic tools.

### Metabolic predictors

Three articles included in the review examined the prognostic value of diurnal cortisol dynamics. The article by Cosgriff et al. (1990) found that higher average daytime cortisol levels were associated with a higher risk of relapse in patients with clinical recovery after ECT. A study by Vrshek-Schallhorn et al. (2013) identified cortisol awakening response (CAR) as an important predictor of manifest and subsequent relapses of major depressive episodes (MDE) in young individuals. CAR showed predictive power for up to 30 months, with a decline in prognostic strength over time. Hardeveld et al. (2014) investigated the prognostic value of cortisol metabolism indicators, including CAR, DST, and evening cortisol levels, in a large sample of individuals with remitted major depressive disorder (MDD). The study revealed that high CAR was associated with a higher risk of relapse, while total daily cortisol and negative feedback mechanisms were not associated with relapse. The analysis did not support the assumption that higher CAR indicates hypersensitivity to psychosocial stress. Although CAR is not currently used as a diagnostic instrument or biomarker in a clinical setting, it is considered a valuable tool in research studies.

### Chronotherapeutic predictors

The only study, included into the review, that is devoted to chronotherapy as predictor of recurrence studied LT effects when treating winter type SAD (Meesters et al. 1993). Frequency of repeated relapses of depression during remaining part of winter after treatment was 54%. Since randomization of experimental group concerned LT type (morning and evening), the results don't allow to evaluate the influence of this method of treatment on relapses in regard to clinical groups that haven't undergone LT. However, authors conclude that relapse can be prevented during remaining winter season if the treatment is done in the very first stage of depression manifestation.

## DISCUSSION

Methodological approaches to studying depression prognosis have been extensively researched, as outlined in the recent review by Moriarty et al. (2021). However, this detailed systematic review did not mention chronobiological predictors of depressive relapses. The majority of the reviewed prognostic models differed in their predictors, conditions, and populations, and most studies were marked as having a high risk of systematic error. It is concluded that there is limited data available to predict individual depression relapse risk in clinical practice. Further research is needed to develop reliable predictors using higher-quality studies and different combinations of predictors. Several studies related to chronobiological indicators were excluded from the review but are of interest. For example, a study by Leerssen et al. (2020) plans to assess the impact of cognitive behavioral therapy and chronobiological therapy on the risk of developing depressive states in individuals with insomnia. Filippis et al. (2020) evaluated the association between calcium imbalance, parathyroid hormone levels, and chronotype in relation to bipolar disorder severity. Although the meta-analysis by Au & Reece (2017) did not focus on developing prognostic models, it provides valuable material for further analysis. Additionally, Takaesu (2018) conducted a detailed review on circadian system, chronotype, insomnia, and other chronobiological factors in bipolar disorder. Studies on cortisol secretion have been more extensive, but some

may not have been captured in the systematic search due to their early publication dates. CAR has been a focus in recent studies due to its close link to circadian system synchronization. In our own original research (Strelnik 2014) examined the use of macrorhythms in predicting depression relapses, considering multi-month and multi-year rhythmic fluctuations. These rhythms are ecological-chronobiological in nature, and their connection to environmental factors requires further investigation. The study emphasizes the importance of clinical and etiopathogenetic verification, as the profiles of macrorhythms differ across various nosologies. Cultural influences and international differences are also highlighted in Kasof's review (2009), suggesting their potential role in seasonal affective disorder (SAD) etiology.

## CONCLUSIONS

The possibilities of developing a precise and practical model for predicting depression relapse and recurrence remains limited. The chronobiological approach allows for a chronological prognostic model, indicating the time period of maximum relapse risk. Prognostic models without chronological predictors only indicate the general risk of depression throughout life. Certain circadian indicators, such as heart rate, physical activity, light exposure, bedtime, and waking up time, show high accuracy in predicting relapse, with detected instability being a significant prognostic factor. Digital technologies, including AI, machine learning algorithms, smartphone apps, and wearable devices, enhance the accuracy of prediction and enable proactive interventions. The prognostic significance of relapse seasonality is uncertain due to inconsistent findings. Other chronobiological factors, such as cortisol awakening response, diurnal cortisol secretion, insomnia subtypes, individual chronotype, mood fluctuations, and long-term circannual rhythms, have potential as predictors and require further study. Evaluating the effectiveness of integrated prognostic models incorporating various factors, both chronobiological and non-chronobiological, warrants further research. The use of digital technologies holds promise in data collection and mathematical processing for an improved prognostic model of recurrence.

### Limitations of the study

As far as we know, our review is the first attempt at descrinig the most complete aggregate of chronobiological predictors of depression relapse, suited for modeling further course (recurrence) of affective disorder.

In search systems we couldn't always get in a sample works that we know, that match the aim of review and that are present in database. This is due to the lack of uniform research terminology, which in turn is due to methodological and terminological blanks in the area of mental disorders chronobiology. Partially this limitation was possible to bypass by forming quite complex and detailed search query and by additional search in different bases and bibliographic lists of examined original studies and reviews. These limitations also reflect potential presence of some number of works on this subject that weren't analyzed in this review.

From the search results were excluded for analysis articles about other chronobiological factors and biorhythms due to the fact that they haven't been addressed by researchers in the term of relapse prognosis, though it is impossible to deny their potential prognostic value (for example, we haven't find any studies of multi-year macrorhythms of recurrence apart from our own research). Analysis of the results of examined studies allowed to outline a list of potentialy the most significant chronobiological predictors that have value for certain parameters of depression course prognosis and that we listed in the discussion. However, great variety of methodological approaches, toolkit, design, lack of high quality studies in analyzed articles in general makes their results not comparable in quantitative terms and defines impossibility of direct comparison of 'proportion' of chronobiological parameters in terms of prognosis of manifest, worsening or relapse of depression. Bringing together described chronobiological factors with the aim of studying their total and specific value for depression course prognosis should become the aim of future studies.

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### *Conflict of interest:*

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### *Contribution of individual authors:*

Sergey Strelnik & Anna Strelnik formulated the working hypothesis, inclusion criteria and search algorithm for the review, were responsible for the literature search and wrote the first draft of the manuscript.

Darya Astafeva & Dmitry Romanov contributed to the supervision in the data analysis, writing and editing of the manuscript. All authors approved the final version of the article before its submission.

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