Depression: An actionable outcome for those at clinical high-risk

Jean Addington [a,*], Megan S. Farris [a], Lu Liu [a], Kristin S. Cadenhead [b], Tyrone D. Cannon [c], Barbara A. Cornblatt [d], Thomas H. McGlashan [e], Diana O. Perkins [f], Larry J. Seidman [g], Ming T. Tsuang [b], Elaine F. Walker [h], Carrie E. Bearden [i], Daniel H. Mathalon [j], William S. Stone [g], Matcheri Keshevan [g], Scott W. Woods [e]

[a] Hotchkiss Brain Institute, Department of Psychiatry, University of Calgary, Calgary, Alberta, Canada
[b] Department of Psychiatry, UCSD, La Jolla, CA, United States of America
[c] Department of Psychology, Yale University, New Haven, CT, United States of America
[d] Department of Psychiatry, Zucker Hillside Hospital, Long Island, NY, United States of America
[e] Department of Psychiatry, Yale University, New Haven, CT, United States of America
[f] Department of Psychiatry, University of North Carolina, Chapel Hill, NC, United States of America
[g] Department of Psychiatry, Harvard Medical School at Beth Israel Deaconess Medical Center and Massachusetts General Hospital, Boston, MA, United States of America
[h] Departments of Psychology and Psychiatry, Emory University, Atlanta, GA, United States of America
[i] Semel Institute for Neuroscience and Human Behavior, Departments of Psychiatry and Biobehavioral Sciences and Psychology, UCLA, Los Angeles, CA, United States of America
[j] Department of Psychiatry, University of California, San Francisco, San Francisco, CA, United States of America

ARTICLE INFO

ABSTRACT

Comorbid diagnoses are common in youth who are at clinical high-risk (CHR) for developing psychosis, with depression being the most common. The aim of this paper is to examine depression over two years in a large sample of CHR youth who do not make the transition to psychosis, considering both categorical and dimensional ratings of depression severity. The sample consisted of 267 CHR youth who were followed for two years. Based on DSM-IV diagnoses over this time period, 100 CHR individuals never received a diagnosis of depression, 64 individuals continuously met criteria for depression, 92 individuals received a diagnosis of depression at one or more timepoints, and 11 participants had a diagnosis of depression only at 24-months. These groupings were supported by six-monthly ratings on the Calgary Depression Scale. The majority of this sample experienced a major depressive episode on more than one occasion, suggesting that depression and depressive symptoms identify a domain of substantial unmet clinical need. Recommendations are that depression in CHR youth and young adults should be monitored more frequently and that there is a need for clinical trials to address depression systematically in this vulnerable population.

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1. Introduction

Typically, the goal of research into clinical high-risk (CHR) for psychosis has been to prevent the transition to psychosis. Although there have been some promising outcomes in terms of preventive treatments (Addington et al., 2020), one of the barriers to successful treatment has been the heterogeneity of CHR individuals. Several years ago, research suggested that transition to a psychotic illness occurred in approximately 25% of CHR individuals (Fusar-Poli et al., 2012) but numbers cited in more recent studies suggest that this number is dropping (Addington et al., 2020; Fusar-Poli et al., 2017; Raballo et al., 2020). Unfortunately, this likely does not reflect improved outcomes (i.e., fewer people developing psychosis due to treatment), but rather indicates a highly heterogeneous course with these young people having a range of outcomes often with unmet clinical needs (Addington et al., 2019b; Allswede et al., 2020; Healey et al., 2018; Woods et al., 2018). In addition to experiencing attenuated psychotic symptoms, a decline in functioning (Fusar-Poli et al., 2015), neurocognitive difficulties (Seidman et al., 2016), and comorbid diagnoses are prevalent in this population (Addington et al., 2017), with the most common diagnosis in CHR individuals being depression. Approximately 40–60% of CHR individuals report a current or past depressive episode (Addington et al., 2017; Fusar-Poli et al., 2014; McAusland et al., 2017; Shi et al., 2017). In addition, depression has been shown to be associated with lower quality of life (Takahashi et al., 2017), more pronounced negative and general symptoms, a decreased likelihood for remission from CHR status (Kline et al., 2018) and to predict persistent paranoia in CHR individuals (Salokangas et al., 2016).

It is still relatively unknown whether or not depression or depressive symptoms are an independent risk factor for transition to psychosis, or, what might be more likely, a marker of poor prognosis for the CHR syndrome (Kline et al., 2018). Kline and colleagues (Kline et al., 2018)

* Corresponding author at: Mathison Centre for Mental Health Research and Education, 3280 Hospital Dr NW, Calgary, AB T2N 4Z6, Canada.
   E-mail address: jmadding@ucalgary.ca (J. Addington).

further suggest that since depression accounts for much of the variation in presenting symptoms of a CHR individual, with the exception of attenuated psychotic symptoms, targeting depression may not only improve depression but other concerns such as general or disorganized symptoms or even poor social functioning. This is important as depression has not been emphasized in the literature as an independent treatment target for CHR individuals, (Addington et al., 2019a) although it is highly prevalent even amongst those who do not transition to psychosis (Addington et al., 2019b).

Finally, to date, depression has mainly been assessed at baseline and less often as a later outcome. Thus, little is known about the trajectory of depression in CHR. Therefore, in attempting to deconstruct the heterogeneity of the CHR syndrome to better predict individual clinical trajectories, examining depression over time is warranted and would be an important clinical outcome to define and address, especially since details on treatment of depression in CHR are limited.

Thus, as a first step to address the heterogeneity of outcomes of CHR youth, this paper will focus on depression as an outcome that could potentially be a marker of poor prognosis (Kline et al., 2018) and which needs to be addressed. More specifically, the paper will focus on assessing the occurrence of depression over a two-year period in those who do not transition to psychosis using both categorical and dimensional ratings of depression.

2. Materials and methods

2.1. Participants

Participants in this study were from the North American Prodrome Longitudinal Study-2 (NAPLS-2). We have previously described in detail our ascertainment processes (Addington et al., 2012). There were 764 CHR participants (436 males, 328 females) in NAPLS-2, recruited from all eight NAPLS-2 sites. The Structured Interview for Psychosis-risk Syndromes (SIPS) (McGlashan et al., 2010) was used to determine if participants met the Criteria for at least one of the Psychosis-risk Syndromes (COPS), that is attenuated psychotic symptoms syndrome (APSS); brief intermittent psychotic symptoms syndrome (BIPS); or genetic risk and deterioration syndrome (GRD). From this NAPLS-2 sample of 764, there were 86 who had transitioned to psychosis, 390 dropped out before two years for various reasons and 21 who did complete two years were excluded from the analyses as they were missing the depression assessments. We have previously demonstrated that there were no clinical differences between those who completed the study and those who dropped out prior to two years (Stowkowy et al., 2018). We have also previously reported that there was minimal depression (less than 4%) reported over time in the healthy control group that was part of NAPLS-2 (Addington et al., 2012; Addington et al., 2017). Thus, the sample ($n = 267$) described in this paper had not made the transition to psychosis and had completed two years of follow-up. Those who made a transition to psychosis were not included since 71 of them converted prior to 12-months and had only baseline DSM-IV diagnoses. Participants' age ranged between 12 and 35 years. Exclusion criteria were meeting criteria for a current or past axis I psychotic disorder, IQ less than 70, or past or current history of a clinically significant central nervous system disorder.

2.2. Measures

Current and lifetime depression was assessed with the Structured Clinical interview for DSM-IV (SCID) (First et al., 1995) and the SIPS (McGlashan et al., 2010) to determine COPS criteria. The severity of attenuated psychotic symptoms was assessed with the Scale of Psychosis-risk Symptoms (SOPS).

The Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1990) was used to measure current depressive symptom severity over the past two weeks. The CDSS was originally developed for patients with schizophrenia to address the issue of the overlap between depression and negative symptoms and has become the recommended scale to assess the severity of depression in schizophrenia (Collaborative Working Group on Clinical Trial Evaluations, 1998). Over the past 20 years there has many published studies on the CDSS (www.ucalgary.ca/cdss) including its translation into more than 40 languages. Its psychometric properties are excellent and include internal consistency, inter-rater reliability, sensitivity, specificity, and discriminant and convergent validity (Addington et al., 1994; Addington et al., 1992; Bernard et al., 1998; Lancon et al., 2000; Muller et al., 1999; Sarro et al., 2004). There is little overlap with positive and negative symptoms (Addington et al., 1994; Muller, 2002). Finally, the CDSS has been shown to be superior relative to other depression rating scales, such as the Hamilton Depression Rating Scale and the Montgomery-Asberg Scale in that it differentiates between depression and negative and positive symptoms and it is short to administer (Addington et al., 1996; Collins et al., 1996). More recently the CDSS has been validated in CHR individuals (Addington et al., 2014).

Social and role functioning were assessed with the Global Functioning-Social (GF:S) and Role (GF:R) scales which were specifically designed to measure social and role functioning in CHR individuals. They have good psychometric properties and construct validity (Cornblatt et al., 2007).

Use of anti-psychotic and anti-depressant medication was determined at each assessment. Participants acknowledged only whether they were taking either of these medications at the given assessments. Data reflecting type, dose, length of use, compliance, and reason for prescription is not available.

2.3. Procedures

This study was approved by the Institutional Review Boards of all eight NAPLS-2 sites. We obtained written informed consent, including parental consent, from all participants 18 and older and parents/guardians of minors. CDSS data were collected at five-time points: baseline, 6-, 12-, 18- and 24-month follow-ups, and SCID diagnoses were conducted annually at baseline, 12- and 24-month follow-ups.

2.4. Statistical analysis

To accommodate missing data and account for intra-participant correlation over time, a generalized linear mixed model for repeated measures was used for the different depression groups to examine changes in CDSS over time (baseline, 6-, 12-, 18-, and 24-months) both between and within depression groups. Two assessments were missing at baseline, 29 at 6-months, 21 at 12-months, 62 at 18-months and 1 at 24-months. One-way Anovas were used to compare each of the depression groups on positive symptoms, negative symptoms and social functioning at each of the five assessment timepoints.

3. Results

Demographics are presented in Table 1. Antipsychotics were used by this sample at different times over the course of two years. Sixty-six percent never used an antipsychotic. Antipsychotics were reportedly being used at all five assessment points by 4.9%, at four assessment points by 4.9%, at three assessment points by 6.4%, at two assessment points by 6.4% and only at one assessment point by 11.2%.

Using the Structured Clinical interview for DSM-IV (SCID) diagnoses of depression (i.e., major depressive disorder, dysthymia and depression NOS) conducted at baseline, 12- and 24-months, four different depression groups were created. No participant had bipolar depression or a mood disorder with psychotic features. These groups were based on the number of assessments at which participants had received a mood diagnosis and considered whether they had received a mood diagnosis at the final assessment at 24-months. Group one consisted of 100

Table 1
Baseline demographic characteristics.

Variable	Total $n = 267$
	Mean (SD)
Age (years)	18.87 (4.37)
Years of education	11.48 (2.74)
	Frequency (%)
Sex	
Female	116 (43.4)
Male	151 (56.6)
Race	
Caucasian	154 (57.7)
Black	53 (19.9)
Interracial	35 (13.1)
Asian	19 (7.1)
Other[b]	6 (2.2)
Marital status	
Single, never married	257 (96.3)
Other	10 (3.7)
Current living arrangement	
Living with family	196 (73.4)
Living with others[a]	41 (15.4)
Living on own	19 (7.1)
Living with spouse/partner	11 (4.1)
Current employment	
Not worked in the past year	131 (49.1)
Currently working	73 (27.3)
Worked in the past year	61 (22.8)
Full time parent	2 (0.7)

Abbreviations: SD, standard deviation.
[a] Includes living with friends (excluding spouse/partners), in a boarding/group home, or academic residence.
[b] Includes, First Nations, Native Hawaiian or Pacific Islander.

individuals who never received a diagnosis of depression at any of the three SCID assessments called NON-DEP. Group two, CON-DEP, consisted of 64 individuals who had a mood diagnosis at 24-months plus a diagnosis of depression at least one other assessment. The majority had received a mood diagnosis on at least 2 occasions prior to 24-months. Group three consisted of 92 individuals who received a diagnosis of depression, at least once, although approximately 50% had a diagnosis at more than one assessment, but had no diagnosis of depression at 24-months called INT-DEP. There were 11 participants who had a diagnosis of depression only at 24-months. We created a separate group for them called 24-DEP as it was unclear in which of the other two groups, they would best fit.

Results of the generalized linear model for changes in CDSS over time and within and between the four depression groups are presented in Table 2 and Fig. 1. For the NO-DEP group, there was significant improvement at 18- and 24-months relative to their baseline scores, although the mean score at baseline was relatively low. For the CON-DEP group, their 6-, 12- and 18- month follow-up scores were significantly decreased with average scores in the moderate range. For those in the INT-DEP group, scores were significantly improved at all follow-up assessments compared to baseline. For the participants in the 24-DEP group there was no statistically significant changes over time in their CDSS scores although there was a notable clinical increase from 12 months to 24 months. With respect to the between group differences it was observed that at each timepoint ratings were significantly higher for the CON-DEP group compared to the NON-DEP group. At baseline, the INT-DEP group also had significantly more severe ratings than the NON-DEP group. Those in the INT-DEP group at both 18-and 24-month follow-up had significantly lower ratings than the CON-DEP group.

The four groups were compared on positive and negative symptoms and social and role functioning at each of the five assessment timepoints (see Table 3). There were no differences between the groups in positive symptoms and role functioning. The CON-DEP group had significantly more severe negative symptoms compared to the NO-DEP group at four of the assessments including 24-months, and to the INT-DEP group at 24-months. There were a couple of differences in social functioning in that the INT-DEP group at baseline and the CON-DEP group at 24 months had significantly poorer social functioning than the NO-DEP group.

Data on whether an individual was taking an antidepressant or not at any assessment was collected. We do not know the reason for the prescription, the type, dose or compliance. However in the NO-DEP group on average 20% reported taking an antidepressant at any one time, for the INT-DEP on average 36% reported taking an antidepressant at each of the assessments and for the CON-DEP approximately 44% were reportedly taking an antidepressant at each time period. For the 24-DEP only a couple were taking an antidepressant prior to 24 months at which time 5 were on an antidepressant. These data are presented in Supplementary Table 1.

4. Discussion

The purpose of this paper was to show that in attempting to deconstruct the heterogeneity of CHR outcome that depression is an

Table 2
Generalized linear models for changes in Calgary Depression Scale over time between and within groups.

CDSS assessment	No depression NO-DEP	Depression at each assessment CON-DEP	1–2 episodes of depression INT-DEP	Depression only at 24 months 24-DEP
	M (SE)	M (SE)	M (SE)	M (SE)
Baseline	4.31 (0.47)	8.30 (0.59)[a***]	7.28 (0.49)[a**]	3.00 (1.42)
6-months	2.69 (0.39)	5.69 (0.49)[b***,h**]	4.05 (0.41)[h***]	4.24 (1.22)
12-months	2.46 (0.37)	5.39 (0.47)[c***,h**]	3.47 (0.38)[h***]	1.55 (1.08)
18-months	2.23 (0.40)[h*]	5.97 (0.51)[d***,h*]	3.30 (0.41)[f**,h***]	2.57 (1.14)
24-months	2.18 (0.36)[h**]	6.47 (0.45)[e***]	2.33 (0.38)[g***,i*]	5.36 (1.10)

M* represents the least squares means estimated by the Generalized linear models.
SE represents the standard error of the mean.
[a] Significantly different from *no depression* group at baseline.
[b] Significantly different from *no depression* group at 6-months.
[c] Significantly different from *no depression* group at 12-months.
[d] Significantly different from *no depression* group at 18-months.
[e] Significantly different from *no depression* group at 24-months.
[f] Significantly different from *depression* group at 18-months.
[g] Significantly different from *depression* group at 24-months.
[h] Significantly different within group change from baseline.
[i] Significantly different within group change from 6-months.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

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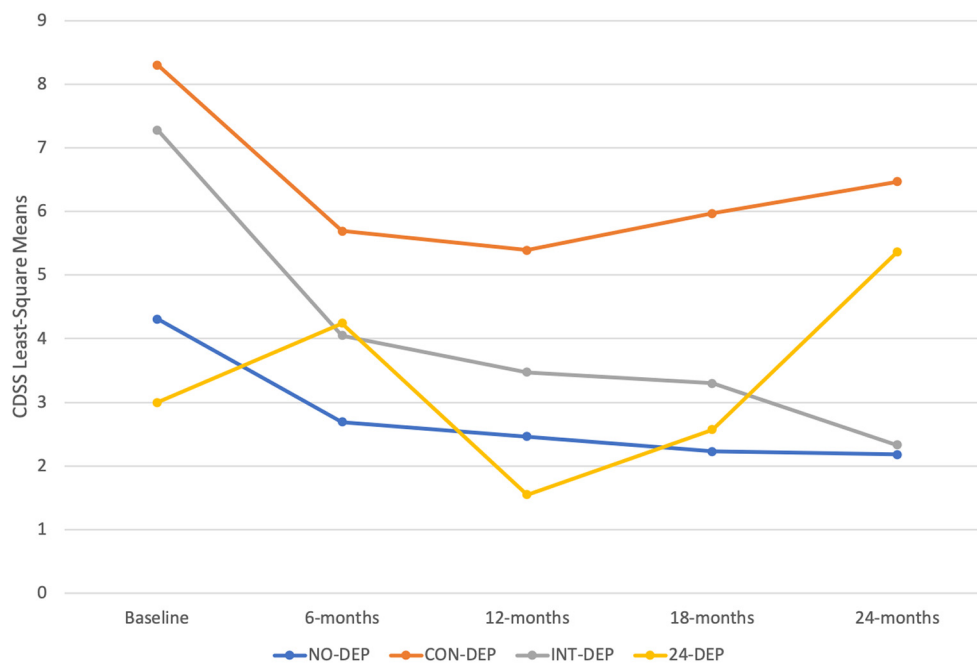
Fig. 1. CDSS scores by depression groups over time.

important outcome that needs to be assessed and treated. To do this we examined depression over the course of two years in a sample of CHR individuals who had not transitioned to psychosis. Based on DSM-IV diagnoses that were conducted at baseline, 12- and 24- month follow-up assessments, we found four distinct depression groups. One group that presented with a diagnosis of depression at 24-months as well as at prior assessments (CON-DEP, $n = 64$), a second group had intermittent periods of depression but were not depressed at the 24-month follow-up (INT-DEP, $n = 92$), a small group who had never previously been depressed but met criteria for depression at the 24-month follow-up (24-DEP, $n = 11$) and those who never met criteria for current depression during the study (NO-DEP, $n = 100$). Thus, there is evidence of a high prevalence of depression over a two-year period with approximately one-third of those who had not transitioned to psychosis having no evidence of depression. The remainder of the sample reported at least one episode of an MDD. What is interesting is that if these young people had

Table 3
Symptomatic and functional differences over time for the four depression groups.

Measure	No depression NO-DEP	Depression at each assessment CON-DEP	1–2 episodes of depression INT-DEP	Depression only at 24 months 24-DEP	Test statistic F
SOPS positive					
Baseline	11.96 (0.42)	11.55 (0.52)	11.70 (0.44)	11.55 (1.26)	0.148
6-months	8.19 (0.46)	8.48 (0.58)	7.86 (0.49)	10.38 (1.39)	1.084
12-months	7.72 (0.49)	7.95 (0.61)	7.26 (0.50)	8.52 (1.46)	0.468
18-months	6.37 (0.48)	7.15 (0.60)	6.14 (0.49)	7.92 (1.40)	0.924
24-months	6.40 (0.46)	7.70 (0.58)	6.12 (0.48)	7.64 (1.39)	1.781
SOPS negative					
Baseline	10.29 (0.59)	14.20 (0.74)[a]	12.35 (0.61)	11.00 (1.77)	5.741[**]
6-months	7.89 (0.59)	10.64 (0.75)[a]	9.13 (0.63)	11.28 (1.8)	3.691[*]
12-months	7.43 (0.57)	10.66 (0.72)[a]	8.35 (0.59)	8.61 (1.73)	2.992[*]
18-months	7.06 (0.61)	9.89 (0.77)	7.93 (0.63)	8.17 (1.79)	1.878
24-months	7.08 (0.57)	9.98 (0.72)[a]	7.25 (0.6)[b]	9.09 (1.73)	4.048[**]
GF:S					
Baseline	6.50 (0.16)	5.95 (0.2)	5.9 (0.16)[a]	6.45 (0.47)	2.920[*]
6-months	6.81 (0.16)	6.33 (0.2)	6.37 (0.16)	6.43 (0.47)	1.455
12-months	7.03 (0.16)	6.32 (0.2)	6.39 (0.16)	7.01 (0.47)	2.363
18-months	7.14 (0.16)	6.35 (0.2)	6.52 (0.17)	6.73 (0.47)	2.513
24-months	7.07 (0.15)	6.34 (0.19)[a]	6.93 (0.15)	6.18 (0.45)	3.934[**]
GF:R					
Baseline	6.47 (0.22)	5.91 (0.27)	6.06 (0.23)	6.09 (0.66)	1.027
6-months	6.59 (0.22)	6.01 (0.28)	6.94 (0.23)	6.09 (0.66)	1.757
12-months	6.72 (0.22)	6.33 (0.27)	6.77 (0.22)	6.60 (0.65)	0.155
18-months	6.49 (0.25)	6.18 (0.32)	6.63 (0.26)	6.32 (0.72)	0.213
24-months	6.32 (0.25)	6.09 (0.31)	6.63 (0.25)	6.82 (0.74)	0.666

Abbreviations: GF:S, Global Functioning: Social Scale; GF:R, Global Functioning: Role Scale; SOPS, Scale of Psychosis risk.
[a] Significantly different from No Depression group.
[b] Significantly different from Depression at Each Episode group.
[*] $p < 0.05$.
[**] $p < 0.01$.

been in one of the newer transdiagnostic studies examining risk for a serious mental illness, approximately 50% of this sample would be considered to have made the transition to a serious mental illness.

We used the CDSS ratings to monitor depression at six-monthly intervals. Results of these ratings offer some support to the allocation of participants to the different depression groups. Both the NO-DEP and CON-DEP groups demonstrated statistically, but not clinically significant improvement over time. The INT-DEP group demonstrated both statistically and clinically significant improvement at each follow-up assessment compared to baseline. The between group differences are also what would be expected at each follow-up.

Interestingly the four groups did not differ on role functioning, nor on positive symptoms at any of the assessment points. There were differences between the NO-DEP and CON-DEP groups at four of the five assessments with the CON-DEP group having more severe negative symptoms. The CON-DEP group also had more severe negative symptoms than the INT-DEP group at 24-months. There were a couple of significant differences in social functioning in that the NO-DEP group had improved social functioning compared to the INT-DEP group at baseline and to the CON-DEP group at 24 months, although these differences could be attributed to type II error. The lack of difference between the groups in positive symptoms suggest that the presence of positive symptoms is unrelated to depression and that they are potentially independent an issue that has long been debated in the schizophrenia field. The only notable significant difference in social functioning was that the CON-DEP had lower ratings than the NO-DEP at 24 months. These differences may just be by chance or it may be that those with more depression do have poorer functioning but there is a possible floor effect since it has been established even when CHR participants are in remission and have improved functioning relative to those who remain symptomatic, their functioning is still poorer than healthy controls (Addington et al., 2019b). Thus, poor functioning would be expected in all groups. It is possible that many with more frequent depression are having difficulty in functioning, and in fact at 24 months there is a small but statistically significant correlation between ratings on the CDSS and the GF:S ($r = -0.36, p < 0.01$). This suggests that our trajectory groupings are too broad to capture the specific association between functioning and depression.

There are several limitations in this paper. First, assessments were limited. DSM-IV diagnoses were only conducted at annual visits and depression ratings at six-monthly interviews. More frequent assessment of depression is needed to truly mark its course over time. Ideally depression with for example the CDSS should be being monitored every 2–4 weeks. However, this study supports a combination of conducting both a DSM diagnostic interview in conjunction with more frequent ratings on a scale such as the CDSS which has been identified as valid for this population and one of the most widely used depression scales in clinical trials. Secondly, a major limitation in this paper, is treatment for depression. This was a naturalistic study, and although participants did receive antidepressants at various times over the 24-months, they were not routinely prescribed in a systematic way, but rather such treatments were left to the discretion of their physicians in the community. It is unknown the reasons why they might be taking an antidepressant or the type and dose. It is possible that they may even have been given an antipsychotic for depression. The same is true for psychological therapies in that even if participants received, for example CBT, it is unknown for what problems the treating clinician was offering CBT. Even if treatment was being offered it may be that some participants were receiving inadequate treatment for their depression. Finally, it is impossible to tell over the course of the 24-month follow-up whether presenting attenuated psychotic symptoms may be due to a mood diagnosis and would possibly remit with adequate treatment, or whether the mood disorder was comorbid to the attenuated psychotic symptoms. This limitation underscores the need for proper trials to address depression in CHR.

In conclusion, this paper supports that depression is a major concern for youth at CHR for psychosis and that it needs to be addressed

as a significant outcome in CHR. Depressive diagnoses are common, and a pattern of consistent depression diagnoses over time may be associated with an unfavorable outcome at 24 months. Recommendations for future studies are that depression must be monitored more closely with far more frequent assessments than occurred in this study. This would allow for a clearer determination of different trajectories which ought to be data driven. Treatment should be offered as part of a controlled trial so that improvements in depression can be accounted for. At the very least careful and frequent monitoring of treatments need to occur. Recent innovations from the National Institute of Mental Health (NIMH) offer promise for the future. Finding preventive treatments for psychosis is an aim of the NIMH Accelerating Medicine Partnership between industry, investigators and government which may include addressing serious mood disorders. Secondly, recent funding opportunities from NIMH that propose to establish large research networks encompassing many international sites that will rapidly recruit large numbers of CHR individuals in order to dissect the heterogeneity and predict differential outcomes to inform future treatment development, offers hope that serious depression in these young people can be assessed, monitored and eventually treated effectively.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2020.10.001.

CRediT authorship contribution statement

Drs. Addington, Cannon, Cadenhead, Cornblatt, McGlashan, Perkins, Seidman, Tsuang, Woods, Walker, Mathalon, and Bearden were responsible for the design of the study and for the supervisions of all aspects of data collection. Ms. Liu was responsible for the statistical analyses. Ms. Farris was responsible for the literature review. Dr. Addington wrote the initial manuscript with help from Ms. Farris. All authors listed have contributed to and approved the final manuscript.

Declaration of competing interest

The authors have declared that there are no conflicts of interest with respect to this paper.

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