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Comorbid Diagnoses for Youth at Clinical High Risk of Psychosis

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Author Conflicts of Interest

Dr. Cannon reports that he is a consultant to the Los Angeles County Department of Mental Health and to Boehringer Ingelheim Pharmaceuticals.

Dr. Woods reports that since 2005 he has received investigator-initiated research funding support from UCB Pharma, Glytech, Lilly, Bristol-Myers Squibb, and Pfizer. He has received sponsor-initiated research funding support from Kali-Duphar, Zeneca, Sandoz, Janssen, Auspex, and Teva and has consulted to Otsuka, Schering-Plough, Merck, Biomedisyn (unpaid), and Boehringer-Ingelheim and has received grants from NIMH, NARSAD, and the Donaghue Foundation. He has also served as an unpaid consultant to DSM-5. He has been granted US patent no. 8492418 B2 for a method of treating prodromal schizophrenia with glycine agonists, is an inventor on a patent pending for a method of predicting psychosis risk using blood biomarker analysis, and has received royalties from Oxford University Press.

All other authors report no conflicts.

Contributors

Cannon, Addington, Bearden, Cadenhead, Cornblatt, Mathalon, McGlashan, Perkins, Seidman, Tsuang, Walker, Wood designed the study and wrote the main study protocol.

Lockwood and Piskulic managed the literature searches.

Liu, Addington and Piskulic managed the statistical approach.

Liu and Piskulic conducted the statistical analyses.

Addington, Piskulic and Lockwood wrote the introduction.

Addington completed the paper.

All authors contributed to and have approved the final manuscript.

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Abstract

Several studies have demonstrated that youth at clinical high risk (CHR) of developing psychosis have a high prevalence of comorbid psychiatric disorders. Less is known about the impact of comorbid diagnoses on later conversion to psychosis and the change over time. The aim of this study was to determine the frequency and distribution of psychiatric diagnoses at baseline and over time in the North American Prodrome Longitudinal Study (NAPLS 2) and the role of comorbid diagnoses in conversion to psychosis. The NAPLS 2 sample consisted of 744 CHR youth and 276 healthy controls. Only 21% of the CHR group did not have a comorbid diagnosis with many have 2–3 DSM-IV comorbid diagnoses. The most common diagnoses were anxiety and depressive disorders, which did improve over time. The only diagnosis at baseline that differentiated the converters from the non-converters was cannabis misuse. Comorbidity, except for cannabis use, was essentially independent of clinical outcome. It is possible that those with comorbid diagnoses are preferentially the help-seeking individuals that present for help in our clinics and research projects and that those who at risk but do not have a comorbid diagnosis may not be seeking help in the prodromal phase.

Keywords

clinical high risk; DSM-IV diagnoses; comorbidity; anxiety; depresssion

1. INTRODUCTION

Studies of young people at high risk of developing psychosis are prominent in the psychosis literature. These young people are at clinical high risk (CHR) of psychosis since the criteria are based on clinical symptoms that include the presence of sub-threshold psychotic symptoms, brief intermittent psychotic symptoms, or the pairing of genetic risk with a decline in functioning (McGlashan et al., 2010; Yung and McGorry, 1996). Interestingly, studies of those at CHR consistently report that these individuals have a high prevalence of comorbid psychiatric diagnoses and, in particular, mood disorders (Fusar-Poli et al., 2013). In the first North American Prodrome Longitudinal Study (NAPLS), the prevalence of any DSM-IV diagnosis of anxiety or depression or both in 377 help-seeking CHR participants was 69% (Woods et al., 2009). In 2012, the European Prediction of Psychosis Study (EPOS) (Salokangas et al., 2012), which included 245 individuals at CHR, reported that 71% of participants were given at least one life-time diagnosis and 62% were assessed as having one or more current diagnoses. Rates of a current depression or anxiety disorder were reported in 34% and 39% respectively of the sample. A more recent study, which included 509 individuals at CHR reported the presence of comorbid Axis 1 diagnoses in 73% of the sample. More specifically 40% had a depressive disorder, either on its own (26%) or with an anxiety disorder (14%), and 8% had only an anxiety disorder (Fusar-Poli et al., 2014).

Additionally, of 226 individuals at CHR who were followed-up between 2 and 14 years following first presentation, 90% of them had a non-psychotic disorder at baseline, which persisted at follow-up for 52% of the sample (Lin et al., 2014). A meta-analysis of 11 studies from 2014 that included 1,684 CHR individuals calculated the prevalence of depression and anxiety disorders as 41% and 15% respectively (Fusar-Poli et al., 2014).

Comorbid diagnoses are of concern in that they have been reported to increase the subjective burden of attenuated psychotic symptoms in those at CHR, and to predict poorer long-term outcomes (Wigman et al., 2012). Notably, the distress of depression and anxiety can overshadow that caused by attenuated psychotic symptoms to such an extent that depression and anxiety are most often the primary complaint when CHR individuals are first seeking help (Falkenberg et al., 2015). Furthermore, their role in later conversion to psychosis has not been conclusively explored. In NAPLS-1, except for substance use, comorbid diagnoses were not associated with conversion to psychosis (Woods et al., 2009). In the EPOS study, current bipolar, somatoform and depressive disorders were shown to predict conversion to psychosis, while anxiety disorders predicted non-conversion to a psychotic disorder (Salokangas et al., 2012). In a meta-analysis, during an average follow-up of 3.7 years, no association was found between additional diagnoses at baseline and conversion to a psychotic disorder in 509 CHR individuals (Fusar-Poli et al., 2014). More recently, emergence of non-psychotic disorders, namely mood and anxiety disorders, was reportedly independent of the psychosis risk status whereby individuals at CHR had the same level of risk as their help-seeking counterparts who did not meet criteria for CHR syndrome or psychosis (Fusar-Poli et al., in press; Webb et al., 2015).

In NAPLS 2, we have previously published on anxiety disorders and substance use. In the first paper, it was reported that 51% of CHR study participants presented with an anxiety disorder but there was no association between baseline anxiety disorder and later conversion to psychosis (McAusland et al., 2015). In the second paper, those at CHR had an increased level of severity of cannabis use with respect to their healthy peers, but did not use cannabis more frequently and no association was reported between cannabis use and later conversion to psychosis (Buchy et al., 2015). However, this paper only focused on ratings of severity and frequency of substance use and not DSM-IV diagnoses.

Here, we focus on the prevalence of Axis I DSM-IV diagnoses in the NAPLS-2 cohort. We have throughout this paper referred to the clinical diagnoses that meet DSM-IV criteria as “comorbid diagnoses”. We appreciate that since the CHR criteria is not an established DSM-V disorder that the use of the term “comorbid” could be misleading. However, it is widely used in the high-risk literature meaning, as we do here, that the individual meets criteria for one or more DSM-IV disorders in addition to meeting the criteria for CHR. The aims of the current study are to determine, first, the frequency and distribution of psychiatric diagnoses at baseline in those at CHR as compared to their healthy peers; secondly, whether there are differences in the baseline prevalence of psychiatric diagnoses between those who developed psychosis and those who did not; and finally, changes in diagnoses over time will be examined.

2. METHODS

2.1 Participants

Participants were recruited as part of the multi-site NIMH funded NAPLS-2 study. CHR participants were help-seeking and were referred from health care providers, educators or social service agencies, or were self-referred in response to community educational efforts. Each site advertised for healthy controls. The NAPLS 2 sample consisted of 764 CHR individuals (436 males, 328 females) and 279 healthy controls (HC) (141 males, 138 females) recruited across the eight NAPLS 2 sites. Study participants were evaluated using the Structured Interview for Psychosis-risk Syndromes (SIPS) (McGlashan et al., 2010) to determine if they met the Criteria of Psychosis-risk Syndromes (COPS) i.e. one or more of the following high risk syndromes: attenuated psychotic symptoms syndrome; brief intermittent psychotic symptoms syndrome; and genetic risk and deterioration syndrome. Seven hundred and forty-three of the CHR participants met Criteria of Psychosis-risk Syndromes (COPS). A further 21 CHR participants were considered high risk due to the presence of schizotypal features and age less than 18 years. Of the total NAPLS 2 sample, 744 CHR and 276 HCs had complete baseline data for the SCID and thus will be the sample described in this paper. Participants had to be between 12 and 35 years of age. Participants were excluded if they met criteria for any current or past axis I psychotic disorder, or had an IQ below 70, or past or current history of a clinically significant central nervous system disorder. HCs were excluded if they had a first-degree relative with a current or past psychotic disorder. We have previously reported a more detailed description of recruitment procedures, ascertainment, and inclusion and exclusion criteria (Addington et al., 2015).

2.2 Measures

The Structured Interview for Psychosis-risk Syndromes (SIPS) (McGlashan et al., 2010) was used to determine whether an individual met COPS criteria. The Scale of Psychosis-risk Symptoms (SOPS) consisting of 19 items in 4 symptom domains (i.e. positive, negative, general, and disorganized symptoms) was used to rate the severity of attenuated psychotic symptoms.

The Structured Clinical interview for DSM-IV (SCID) (First et al., 1995) was used to determine the presence of current and past psychiatric diagnoses, including conversion to a psychotic disorder.

Conversion to psychosis was determined by meeting the Presence of Psychotic Symptoms (POPS) (McGlashan et al., 2010) criteria. POPS requires that at least one of the five SOPS positive symptoms reached a psychotic level of intensity (rated 6) for a frequency of ≥ 1 h per day for 4 days per week, or that symptoms seriously impacted functioning (e.g. disorganizing or dangerous to self or others).

Clinical outcome at each follow-up assessment was determined in the following way: (i) remission (remission from all CHR syndromes, which means scores of 2 or less on all five positive symptoms on the SOPS scale, or for those who have only GRD, “in remission” will require GAF to have returned to 90% of previous best GAF); (ii) symptomatic (not currently meeting criteria for a prodromal risk syndrome but having ratings of 3–5 on any one of the

five positive symptoms on the SOPS, or with the no change in the GAF); (iii) prodromal progression (currently meeting criteria for one of the at risk syndromes; APSS, GRD, BIPS) and (iv) psychotic (currently meeting criteria for a psychotic disorder or evidencing scores of 6 on one or more positive symptoms of the SOPS) (Woods et al., 2014).

2.3 Procedures

Both CHR individuals and HCs were recruited for the study, which was approved by the Institutional Review Boards of all eight NAPLS-2 sites. Written informed consent, including parental consent, was obtained from all adult participants and parents/guardians of minors. After the initial screening assessment that included administering the SCID and the SIPS, vignettes were developed for each CHR participant to obtain a consensus diagnosis. The attenuated psychotic symptoms rated on the SOPS are described at length and include both recent and longstanding symptoms. The vignettes are written so that raters from all eight sites can review the information under each symptom category and provide a reliable rating. Once approved at the site level, the vignette is presented on a conference call for a consensus decision on the symptom ratings as well as the diagnosis. The NAPLS-2 consensus call, chaired by JA, was held once a week and attended by the clinical raters from each of the eight sites. Submitted vignettes are individually reviewed and a consensus must be reached on each symptom rating, diagnosis and ultimate admission into the study. Clinical raters were experienced research clinicians. Gold standard post-training agreement on determining the prodromal diagnoses was excellent (kappa=0.90) (Addington et al., 2012). Diagnostic interviews at all sites were conducted by trained raters. Data were collected at three time points: baseline, one year and two years.

2.4 Statistical analysis

All analyses were performed using IBM SPSS version 23 and SAS 9.4. Between group differences on demographics and DSM-IV diagnoses were analyzed using t-tests and chi-square tests. The generalized estimating equations (GEE) (Liang and Zeger, 1986; Zeger and Liang, 1986) method, an extension of the quasi-likelihood approach (Wedderburn, 1974) is being increasingly used to analyze longitudinal (Diggle et al., 1994) and other (Burton et al., 1998) correlated outcomes data (repeated measurements), especially when they are binary. We used the GEE models to determine change in diagnoses overtime for the CHR participants.

3. RESULTS

3.1 Demographics

There were 744 CHR participants (426 males, 318 females) and 276 HCs (139 males, 137 females). The majority of the sample was white, were students and lived at home. The CHR group was younger, with fewer years or education. A significantly higher proportion of HCs was employed. Baseline demographics are presented in Table 1.

3.2 Conversion

Eighty-six CHR participants converted to psychosis during the two-year study period.

3.3 DSM- IV Diagnoses

Baseline diagnoses were available for 744 CHR and 276 HC participants. For the CHR sample, 401 had SCID diagnoses available at one year and 267 had SCID diagnoses available at 2 years. Since there were multiple diagnoses, often with very low numbers in each individual category, we combined several groups of diagnoses such as all the depression diagnoses, bipolar diagnoses, substances other than cannabis and alcohol, all anxiety disorders except OCD and PTSD, eating disorders and learning disorders. Frequency of these combined diagnoses at baseline and follow-up are presented in Table 2. Frequency of all diagnoses reported are available in Supplementary Table 1.

At baseline, 21% of CHR participants had no diagnoses, 37% had 1, 28% had 2, 10% had 3 and 4% had 4 diagnoses. Results of the group comparisons on the presence of DSM-IV diagnoses at baseline are presented in Table 3. There were significant group differences between CHR and HC in the prevalence of psychiatric diagnoses, with CHR participants having more psychiatric diagnoses overall than HCs at baseline.

Since several participants dropped out before the 12 and 24-month assessment including those who converted, Table 4 describes the change in diagnoses over time from baseline to 24 months for CHR and control participants by using GEE models. After adjusting for the correlated diagnoses data, the results of the GEE modelling demonstrated that improvement in anxiety disorders was observed in that significantly less CHR individuals were diagnosed with an anxiety disorder at 12 months (β =−0.31, SE =0.09, p=0.002, OR = 0.74, 95% CI = 0.59–0.91) and at 24 months (β =−0.42, SE =0.11, p=0.0004, OR = 0.66, 95% CI = 0.51–0.85) when compared to those at baseline. Significantly less CHR individuals were diagnosed with a mood disorder at 24 months (β =−0.45, SE =0.14, p=0.003, OR = 0.64, 95% CI = 0.46–0.88) when compared to those at baseline, and when compared to those at 12 months (β =−0.35, SE =0.12, p=0.01, OR = 0.70, 95% CI = 0.53–0.93). For the healthy controls there was a significant increase in those with a depression disorder from baseline to 12 months.

Since only 267 CHR individuals who had not converted completed the final 24-month assessment, a comparison of their baseline diagnoses with the baseline diagnoses of those who converted demonstrated that those who converted reported significantly more cannabis disorders and more “other substances” disorders. There were no other differences.

Finally, we compared the diagnoses of the different clinical outcome groups at 24 months. By the end of the study 85 participants had converted to psychosis, 106 were in remission from attenuated psychotic symptoms, 87 were still symptomatic and 71 continued to meet prodromal criteria. These groups did not differ on the presence of any disorders at baseline with the exception of anxiety disorder (X^2=13.93, p<0.01). Significantly fewer individuals in the remission group and significantly more individuals in the symptomatic group had an anxiety disorder at baseline than would be expected by chance.

4. DISCUSSION

This paper examined the comorbid diagnoses of a large sample of help-seeking individuals who were at CHR for developing psychosis. The most common diagnoses were depression and anxiety, with 43% of the sample having a diagnosis of depression and 47% having an anxiety disorder with an additional 9% having either PTSD or OCD. Nineteen percent had an attention deficit hyperactivity disorder, with other diagnoses occurring much less frequently. However, almost 80% of this young sample had a comorbid disorder, in that in that only 21% had no comorbid diagnosis and 37% had between two and four axis-1 diagnoses. Improvements over time were noted for anxiety, and depression. Although there was a statistically significant improvement over time for both depression and anxiety more than 30% continued to meet criteria for these disorders at 12 and 24 month follow-ups. This supports the idea that these young people in addition to meeting CHR criteria are a troubled group presenting with many comorbid problems.

When we compared the non-converters who remained in the study and thus, had not converted by 24 months to those who had converted, the proportion using cannabis, although small was significantly different. In our earlier paper on substance use (Buchy et al., 2015) we did not observe differences in converters and non-converters in terms of baseline severity and frequency of cannabis use on the Alcohol and Drug Abuse Scale (Drake et al., 1996). However, a recent meta-analysis (Kraan et al., 2016) supports the notion that it may be more severe use such as that meeting DSM criteria versus ratings of use is what differentiates converters and non-converters with respect to cannabis.

However, one of the most important findings of this study is that comorbidity is largely independent from clinical outcomes in CHR individuals, in that the presence of a comorbid diagnosis at baseline is not necessarily predictive of later conversion to psychosis. It may, however, in further studies be useful to examine other outcomes such as functional outcome as it has been reported in an earlier study that individuals at CHR who did not develop psychosis during the 6-year follow-up but who were otherwise affected by one or more recurrent comorbid disorders presented with poor functional outcomes at follow-up (Rutigliano et al., 2016).

Furthermore, it has been clinically observed that in our high-risk clinics and studies we are not necessarily seeing all the people who eventually develop psychosis. It is possible that the people who also have comorbid diagnoses are preferentially the help-seeking individuals that present for help to our CHR clinics and who participate in our CHR studies. Those who are at CHR for psychosis but do not have comorbid diagnoses may be less likely to seek help in the prodromal phase. It may be that our recruitment methods preferentially capture comorbid individuals and thus elevate the rates. This is supported by recent evidence indicating that recruitment strategies and pretest risk enrichment are significant factors impacting the prognostic accuracy of the CHR instruments (Fusar-Poli et al., 2016a; Fusar-Poli et al., 2016b). CHR individuals who do not have comorbidity may tend to deny illness rather than come for care. If so, they will be a challenge to identify. It is possible that further education on attenuated psychotic symptoms to both the general public, including youth and to mental health professionals may help better identify those whose only symptoms may be

attenuated psychotic symptoms. Finally, if it is the case that the presence of a comorbid disorder is, for some young people who are also at risk for psychosis, the trigger to seek help this supports the need for specialized CHR services versus treating them in regular clinics because of their common mental disorders.

There were two significant limitation in this paper. In this naturalistic study, participants made use of various treatments both psychosocial and pharmacological at various times throughout the course of the study. Treatments may not necessary coincide with the 2–3 assessments of comorbid diagnoses. It was beyond the scope of this paper to describe the exact treatments that occur in conjunction with the diagnoses being made and possible later remission from that diagnoses. However, participants were usually treated as needed for various concerns. The second limitation is that, although it was a large sample, there was a significant drop in the number of participants available at the 12 and 24 month follow-ups.

In summary, the results of this study suggest that youth at CHR for psychosis present with a great deal of comorbidity. However, comorbidity is essentially independent of outcome of psychosis except for cannabis misuse. What is of most concern is that CHR individuals without comorbid diagnoses may be denying illness or at least not seeking help.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Role of Funder

The NIMH had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

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Table 1

Demographic Characteristics for Clinical High Risk and Healthy Control Participants

Variable	Controls *n* = 276	CHR *n* = 744	Test Statistic
	Mean (SD)		*t*
Age in years	19.78 (4.66)	18.52 (4.24)	3.94**
Years of education	12.73 (3.57)	11.30 (2.81)	6.01**
	Number (%)		X^2
Sex			
Male	139 (50.3)	426 (57.2)	3.84
Female	137 (49.6)	318 (42.7)	
Race			
First Nations	4 (1.4)	13 (1.7)	4.85
Asian	30 (10.9)	54 (7.3)	
Black	48 (17.4)	114 (15.3)	
Latin America/Middle East/White	164 (59.4)	466 (62.6)	
Native Hawaiian or Pacific Islander	1 (0.4)	3 (0.4)	
Interracial	29 (10.5)	93 (12.5)	
Marital Status			
Single never married	262 (94.9)	703 (94.5)	0.001
Other	14 (5.1)	38 (5.1)	
Currently working			
Yes	129 (46.7)	185 (24.9)	44.49***
No	147 (53.3)	555 (75.0)	
Currently enrolled as a student			
Yes	223 (80.8)	611 (82.1)	0.375
No	53 (19.2)	130 (17.5)	

* p<0.05,

** p<0.01,

*** p<0.001

Table 2

Prevalence of DSM-IV diagnoses in CHR participants at baseline and at follow-up

Current diagnoses	Baseline n= 744 (%)	12 months n= 396 (%)	24 months n= 267 (%)
Depression Disorder	316 (42.5)	157 (39.9)	86 (32.2)
Bipolar Disorder	50 (6.7)	26 (6.6)	23 (8.6)
Alcohol Misuse	24 (3.2)	18 (4.6)	9 (3.4)
Cannabis Misuse	38 (5.1)	20 (5.1)	17 (6.4)
Other Substances-misuse	7 (0.9)	6 (1.5)	7 (2.6)
Obsessive-Compulsive Disorder	51 (6.9)	20 (5.1)	12 (4.5)
Post-traumatic Stress Disorder	16 (2.2)	6 (1.5)	7 (2.6)
Anxiety Disorder	355 (47.8)	154 (39.2)	100 (37.5)
Somatoform Disorder	8 (1.1)	0 (0.0)	0 (0.0)
Paraphilia	8 (1.1)	3 (0.8)	1 (0.4)
Eating Disorder	9 (1.2)	6 (1.5)	7 (2.6)
Learning Disorder	49 (6.6)	29 (7.4)	27 (10.1)
Attention Deficit Hyperactivity Disorder	130 (17.5)	68 (17.3)	39 (14.6)
Developmental Disorder	19 (2.6)	15 (3.8)	8 (3.0)
Oppositional Defiance Disorder	22 (3.0)	8 (2.0)	2 (0.7)

Table 3

Baseline Comparisons of Clinical High Risk versus Healthy Controls

	Clinical High Risk vs Healthy Controls		
Current SCID Diagnoses	**CHR n= 744 (%)**	**HC n= 276 (%)**	**χ^2**
Depression Disorder	316 (42.5)	4 (1.4)	157.66***
Bipolar Disorder	50 (6.7)	0 (0.0)	19.53***
Alcohol Misuse	24 (3.2)	0 (0.0)	9.13**
Cannabis Misuse	38 (5.1)	2 (0.7)	10.28**
Other Substances Misuse	7 (0.9)	0 (0.0)	2.62
Obsessive-Compulsive Disorder	51 (6.9)	0 (0.0)	19 94***
Post-traumatic Stress Disorder	16 (2.2)	0 (0.0)	6.04*
Anxiety Disorder	355 (47.8)	11 (4.0)	176.69***
Somatoform Disorder	8 (1.1)	0 (0.0)	3.0
Paraphilia	8 (1.1)	0 (0.0)	3.0
Eating Disorder	9 (1.2)	0 (0.0)	3.37
Learning Disorder	49 (6.6)	2 (0.7)	14.61***
Attention Deficit Hyperactivity Disorder	130 (17.5)	5 (1.8)	43.16***
Developmental Disorder	19 (2.6)	0 (0.0)	7.21**
Oppositional Defiance Disorder	22 (3.0)	1 (0.4)	6.17*
Past SCID Diagnoses			
Depression Disorder	266 (35.8)	19 (6.9)	83.33***
Bipolar Disorder	27 (3.6)	0 (0.0)	10.29**
Alcohol Misuse	67 (9.0)	4 (1.4)	17.75***
Cannabis Misuse	82 (11.0)	5 (1.8)	21 89***
Other Substances Misuse	32 (4.3)	2 (0.7)	8.01**
Obsessive-Compulsive Disorder	34 (4.6)	0 (0.0)	13.05***
Post-traumatic Stress Disorder	24 (3.2)	0 (0.0)	9 12**
Anxiety Disorder	201 (27.0)	8 (2.9)	71.88***
Somatoform Disorder	7 (0.9)	0 (0.0)	2.62
Eating Disorder	17 (2.3)	4 (1.4)	0.68
Learning Disorder	36 (4.8)	1 (0.4)	11.56**
Attention Deficit hyperactivity Disorder	111 (14.9)	8 (2.9)	28.29***
Developmental Disorder	18 (2.4)	0 (0.0)	6.82**
Oppositional Defiance Disorder	18 (2.4)	2 (0.7)	3.02

*p<0.05,

** p<0.01,

*** p<0.001

Table 4

Generalized Estimating Equations models for changes in diagnoses over time for CHR and Control participants

	CHR			Control		
SCID diagnoses	**Baseline (N=744) M* (SE)**	**12 months (N= 396) M* (SE)**	**24 months (N= 267) M* (SE)**	**Baseline (N=276) M* (SE)**	**12 months (N= 198) M* (SE)**	**24 months (N= 145) M* (SE)**
Depression Disorder	42.5(0.018)	40.3(0.02)	32.2 (0.03)^{a**b*}	1.4(0.007)	6.4(0.02)a**	3.0(0.01)
Bipolar Disorder	6.7 (0.009)	6.2 (0.01)	7.4 (0.01)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Alcohol Misuse	3.2 (0.006)	4.6 (0.01)	3.2 (0.009)	0.0 (0.0)	0.01 (0.007)	0.0 (0.0)
Cannabis Misuse	5.1 (0.008)	5.5 (0.01)	5.6 (0.01)	0.7 (0.005)	1.6 (0.008)	1.1 (0.007)
Other Substances Misuse	0.9(0.004)	1.5 (0.006)	2.7 (0.009)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Obsessive-Compulsive Disorder	6.9 (0.009)	5.4 (0.001)	3.6(0.001)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Post-traumatic Stress Disorder	2.2(0.005)	1.5(0.006)	2.5(0.009)	0.0 (0.0)	0.5(0.005)	0.5(0.005)
Anxiety Disorder	47.8 (0.02)	40.3 (0.02)^{a**}	37.6 (0.03)^{a***}	3.6 (0.11)	4.5 (0.01)	3.6 (0.01)
Paraphilia	1.1 (0.004)	0.7 (0.004)	0.3 (0.003)	0.0 (0.0)	0.0 (0.0)	0.7 (0.007)
Eating Disorder	1.2 (0.004)	1.5 (0.006)	1.9 (0.009)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Learning Disorder	6.6 (0.009)	5.8 (0.01)	7.3 (0.01)	0.7 (0.005)	0.7 (0.005)	0.7 (0.005)
Attention Deficit Hyperactivity Disorder	17.6 (0.01)	16.6 (0.02)	13.6 (0.02)	1.8 (0.008)	1.0 (0.007)	2.0 (0.01)
Developmental Disorder	2.6 (0.006)	3.6 (0.008)	2.7(0.008)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Oppositional Defiance Disorder	2.9 (0.006)	1.5(0.007)	0.6 (0.005)	0.4 (0.004)	0.4 (0.004)	0.4 (0.004)

M* represents the least squares proportion (%) estimated by the Generalized Estimating Equations models.

SE represents the standard error of the proportion

* p<0.05,

** p<0.01,

*** p<0.001,

**** p<0.0001

^{a} significantly different from baseline,

^{b} significantly different from 12 months.

Table 5

Diagnostic prevalence at baseline between converters and those who completed the 24-month final assessment

Current SCID Diagnoses	CHR-NC n= 267 (%)	CHR-C n= 85 (%)	χ^2
Depression Disorder	117 (43.8)	38 (44.7)	0.21
Bipolar Disorder	22 (8.2)	6 (7.1)	0.12
Alcohol Misuse	8 (3.0)	4 (4.7)	0.57
Cannabis Misuse	7 (2.6)	7 (8.2)	5.32*
Other Substances Misuse	0 (0.0)	2 (2.4)	6.31
Obsessive-Compulsive Disorder	21 (7.9)	9 (10.6)	0.61
Post-traumatic Stress Disorder	7 (2.6)	3 (3.5)	0.19
Anxiety Disorder	134 (50.2)	39 (45.9)	0.48
Somatoform Disorder	3 (1.1)	3 (3.5)	2.27
Paraphilia	3 (1.1)	1 (1.2)	0.00
Eating Disorder	6 (2.2)	0 (0)	1.94
Learning Disorder	24 (9.0)	4 (4.7)	1.61
Attention Deficit Hyperactivity Disorder	53 (19.9)	11 (12.9)	2.07
Developmental Disorder	8 (3.0)	2 (2.4)	0.10
Oppositional Defiance Disorder	10 (3.7)	1 (1.2)	1.40
Past SCID Diagnoses			
Depression Disorder	101 (37.8)	26 (30.6)	1.46
Bipolar Disorder	14 (5.2)	4 (4.7)	0.03
Alcohol Misuse	26 (9.7)	5 (5.9)	1.19
Cannabis Misuse	27 (10.1)	14 (16.5)	2.53
Other Substances Misuse	11 (4.1)	4 (4.8)	0.06
Obsessive-Compulsive Disorder	14 (5.2)	4 (4.7)	0.03
Post-traumatic Stress Disorder	10 (3.7)	3 (3.5)	0.01
Anxiety Disorder	73 (27.3)	23 (27.1)	0.00
Somatoform Disorder	2 (0.7)	1 (1.2)	0.14
Eating Disorder	6 (2.2)	1 (1.2)	0.38
Learning Disorder	13 (4.9)	6 (7.1)	0.60
Attention Deficit hyperactivity Disorder	33 (12.4)	13 (15.3)	0.49
Developmental Disorder	5 (1.9)	3 (3.5)	0.78
Oppositional Defiance Disorder	5 (1.9)	3 (3.5)	0.79

*
p<0.05,

**
p<0.01,

***
p<0.001