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Preliminary communication

A multinational study to pilot the modified Hypomania Checklist (mHCL) in the assessment of mixed depression ☆

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ABSTRACT

Background: Mixed depression is a common, dimensional phenomenon that is increasingly recognized in unipolar and bipolar disorders. We piloted a modified version of the Hypomania Checklist (mHCL-32) to assess the prevalence and clinical correlates of concurrent manic (hypo) symptoms in depressed patients.
Methods: The mHCL-32, Young Mania Rating Scale (YMRS) and Hamilton Rating Scale for Depression (HAMD-24) were utilized in the assessment of unipolar (UP=61) and bipolar (BP=44) patients with an index major depressive episode confirmed by the Structured Clinical Interview for DSM-IV (SCID). Differential mHLC-32 item endorsement was compared between UP and BP. Correlation analyses assessed the association of symptom dimensions measured by mHCL-32, YMRS and HAMD-24.
Results: There was no significant difference between mood groups in the mean mHCL-32 and YMRS scores. Individual mHLC-32 items of increased libido, quarrels, and caffeine intake were endorsed more in BP vs. UP patients. The mHCL-32 active-elevated subscale score was positively correlated with the YMRS in BP patients and negatively correlated with HAMD-24 in UP patients. Conversely, the mHCL-32 irritable-risk taking subscale score was positively correlated with HAMD-24 in BP and with YMRS in UP patients.
Limitations: Small sample size and cross-sectional design.
Conclusion: Modifying the HCL to screen for (hypo) manic symptoms in major depression may have utility in identifying mixed symptoms in both bipolar vs. unipolar depression. Further research is encouraged to quantify mixed symptoms with standardized assessments.

1. Introduction

There is increased recognition of dimensional symptoms of depression and mania that add or even challenge current contemporary categorical diagnostic classifications. For bipolar disorder, the definition of mixed states by DSM-IV requires that diagnostic criteria are met, except time duration, for both major depression and mania simultaneously (American Psychiatric Association, 2000). While mixed mania is a relatively well-recognized clinical entity, mixed hypomania and mixed depression are less studied and understood. Conceptually, mixed depression in bipolar disorder implies subthreshold manic/hypomanic symptoms in a categorical episode of major depression (Benazzi, 2007, 2008; Swann et al., 2009, 2013). While several definitions of mixed depression have been proposed (Biondi et al., 2005; Benazzi, 2007, 2008; Koukopoulos et al., 2005; Maj et al., 2003; Sato et al., 2003; Swann et al., 2009, 2013), validated operationalized set of criteria in the public domain to assess prevalence, longitudinal evaluation, and clinical outcome of mixed depression in bipolar disorder have only been recently

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introduced. The DSM5 has replaced DSM IV TR mixed episode with a mixed-features specifier that can be applied to episodes of unipolar major depression, hypomania or mania (American Psychiatric Association, 2013).

The Hypomania Checklist-32 item (HLC-32) is a self-rating questionnaire to assess the lifetime history of hypomanic symptoms (Angst et al., 2005a). The instrument assesses symptoms in far greater detail than the 13-item DSM IV based Mood Disorders Questionnaire (Hirschfeld et al., 2003) or DSM IV based structured clinical interview (First et al., 1997). The original intent of the HCL-32 was to perform a retrospective symptom review to screen for bipolar disorder, knowing that many depressed patients who present to healthcare providers depressed often do not recognize, minimize or forget past mania or hypomania. The checklist has two subscores: an active-elevated and irritable-risk taking subscales (Bech et al., 2011). As a screening instrument to be used as part of a diagnostic assessment, the optimal cut-off point for discriminating bipolar from unipolar disorder has been reported to be a score of 14 or higher (Angst et al., 2005b; Aydemir et al., 2011; Vieta et al., 2007). The HCL-32 has been translated and validated in Spanish and Turkish (Aydemir et al., 2011; Vieta et al., 2007).

The purpose of this study was to assess the prevalence of concurrent manic (hypo) symptoms in patients with an index episode of major depression utilizing a modification of the HCL-32. The modification would not focus on a lifetime review of symptoms, but rather concurrent symptoms in patients presenting for depression treatment. As such, we piloted the mHCL-32 by changing its primary property from a diagnostic screening instrument to a tool to assess for concurrent mixed symptoms of depression.

2. Methods

This study was IRB approved at all multinational study sites (Turkey, Chile, USA) and was conducted between January 2011 and December 2012. One hundred five treatment seeking in or outpatients were recruited for the study and provided written informed consent. Adult participants age 18–65 met criteria for a major depressive episode as confirmed by Structured Clinical Interview for DSM-IV (SCID; First et al., 1997). Patients with Axis-I diagnoses other than unipolar (UP) or bipolar disorder (BP) that were the primary reasons for clinical evaluation were excluded from the study. At the time of their initial evaluation symptom severity was assessed utilizing the Hamilton Depression Rating Scale for Depression 24 item (HAMD-24, Hamilton, 1960), the Young Mania Rating Scale (YMRS, Young et al., 1978), and the mHCL-32.

The concurrent presence of manic (hypo) symptoms has generally been quantified utilizing YMRS albeit an instrument that was originally operationalized and validated in acute mania. It is routinely used for baseline assessments in patients with bipolar depression to track for treatment emergent switch and more recently, to assess for concurrent mixed symptom. Modification of the HCL-32 was done by converting the probing time frame instruction for question # 3, from "have you ever" to current time commensurate with the HAM-24 and YMRS scales. After the English version's modification approval was obtained from the main author of HCL-32 (Jules Angst), the already validated Spanish and Turkish versions of HCL-32 were also modified.

3. Statistical analysis

To compare clinical and demographic correlates across bipolar and unipolar subjects, *t*-tests or Wilcoxon tests were used for continuous variables, while chi-squared tests were used for binary variables. Sociodemographic and clinical variables were compared between UP and BP groups. Positive response to each item of mHCL-32 as well as the active elevated and irritable risk taking subscales were compared between groups using chi-squared tests; *p*-values are not corrected for multiple testing. Spearman correlations assessed the associations of mHCL-32, the YMRS and HAMD-24 symptom dimensions.

4. Results

One hundred five patients (UP $n=61$, BP $n=44$) were recruited for the study from Turkey (BP $n=23$, UP $n=25$), Chile ($n=12$ BP, $n=20$ UP) and USA (BP $n=9$, UP$=16$). As presented in Table 1, there were no statistically significant differences between BP and UP patients in terms of gender and age. However, the index episode duration of depression was longer in UP patients while the number of prior hospitalizations and depressive episodes were greater in BP patients.

Depressive symptom severity was significantly higher in UP (29.59 ± 8.74) than BP participants (24.63 ± 9.32, $p<0.01$), but there was no significant differences in YMRS (BP 2.37 ± 2.04, UP 2.45 ± 2.07, $p=0.75$) or mHCL-32 scores (BP 7.81 ± 5.26, UP 6.34 ± 4.29, $p=0.12$). The correlation between the mHCL-32 and the YMRS for the total group was significant ($n=105$, $r=0.36$, $p=0.0001$). The rates of positive endorsement of the mHCL-32 question 16 ("*I am more interested in sex, and/or have increased sexual desire*"), 27 ("*I get into more quarrels*") and 29 ("*I drink more coffee*") were significantly higher in BP vs. UP patients while item 25 ("*I am more impatient and/or get irritable more easily*") was higher in UP group (Fig. 1).

As presented in Table 2, there was a positive correlation between mHCL-32 and YMRS scores in both UP and BP groups. However, the "active elevated" sub-item score was positively correlated with YMRS in BP patients and negatively correlated with HAMD in UP patients. Conversely, "irritable risk taking" sub-item scores were positively correlated with HAMD in BPs and with YMRS in UPs.

5. Discussion

To our knowledge, this is the first study to evaluate the feasibility of developing a self-rating instrument for detecting manic (hypo) symptoms in both UP and BP depression. These data suggest that both BP and UP depressive patients experience subsyndromal manic (hypo) symptoms in depression and that there is a moderate degree of correlation between the subjective report of the mHCL-32 and the objective YMRS.

On an item analysis, there was differential rate of endorsement based on bipolar–unipolar dichotomy with bipolar patients endorsing higher rates of increased libido, caffeine intake, and quarrelsome behavior than unipolar patients, while unipolar patients endorsing higher rates of irritability. The differential and opposite correlational analyses of the mHCL-32 subscales of active-elevated and irritable-risk taking with objective ratings of symptom severity needs further follow-up. It has been previously reported that the excitement symptoms (irritability, racing or crowded thoughts psychomotor agitation and talkativeness) defined by Kraepelin (Benazzi, 2008) are more common in BP than UP depression and thought to be associated with bipolarity (Benazzi, 2005; Maj et al., 2003, 2006; Sato et al., 2003; Serretti et al., 2005). However, these data, given the cross sectional design of study and small sample size, do not allow identification of subsyndromal symptoms that are predictive of differential diagnosis or diagnostic conversion. Nonetheless, the emerging evidence would suggest that mixed symptoms are prevalent in both bipolar and unipolar depressions and are associated with a number of features found in treatment resistant patients.

Table 1
Comparison of clinical variables between UP and BP groups (Mean ± SD).

Demographic	UP ($n=61$)	BP ($n=44$)	p-value
Age	41.5 ± 12.5	37.2 ± 11.6	0.056
Gender male, *n* (%)	17 (28%)	17 (39%)	0.245
Clinical			
Index episode duration (weeks)	25.8 ± 38.9	14.6 ± 17.0	0.020*
Age of onset	30.4 ± 13.4	25.0 ± 8.8	0.054
Days since last episode	1048.4 ± 1819.9	355.3 ± 626.7	0.006*
Duration of Illness (years)	11.3 ± 11.9	12.2 ± 9.9	0.218
Depressive episodes	3.7 ± 4.5	6.2 ± 7.0	0.007*
Hospitalizations depression	0.7 ± 1.1	1.0 ± 1.2	0.109
Manic/hypomanic episodes	0.0 ± 0.2	4.8 ± 5.6	< 0.001*
Hospitalizations mania/hypomania	0.0 ± 0.1	1.0 ± 1.3	< 0.001*
Suicide attempts	0.8 ± 1.8	0.8 ± 1.3	0.961
Clinical Ratings			
HAMD	29.59 ± 8.74	24.63 ± 9.32	0.008*
YMRS	2.45 ± 2.07	2.37 ± 2.04	0.767
mHCL-32	6.34 ± 4.29	7.82 ± 5.26	0.127
mHCL-32 sub-scales			
Active elevated	2.56 ± 3.44	3.64 ± 4.08	0.206
Irritable risk taking	2.46 ± 1.75	2.41 ± 1.94	0.838

UP: unipolar depression, BP: bipolar depression, SD: standard deviation.

* $p < 0.05$.

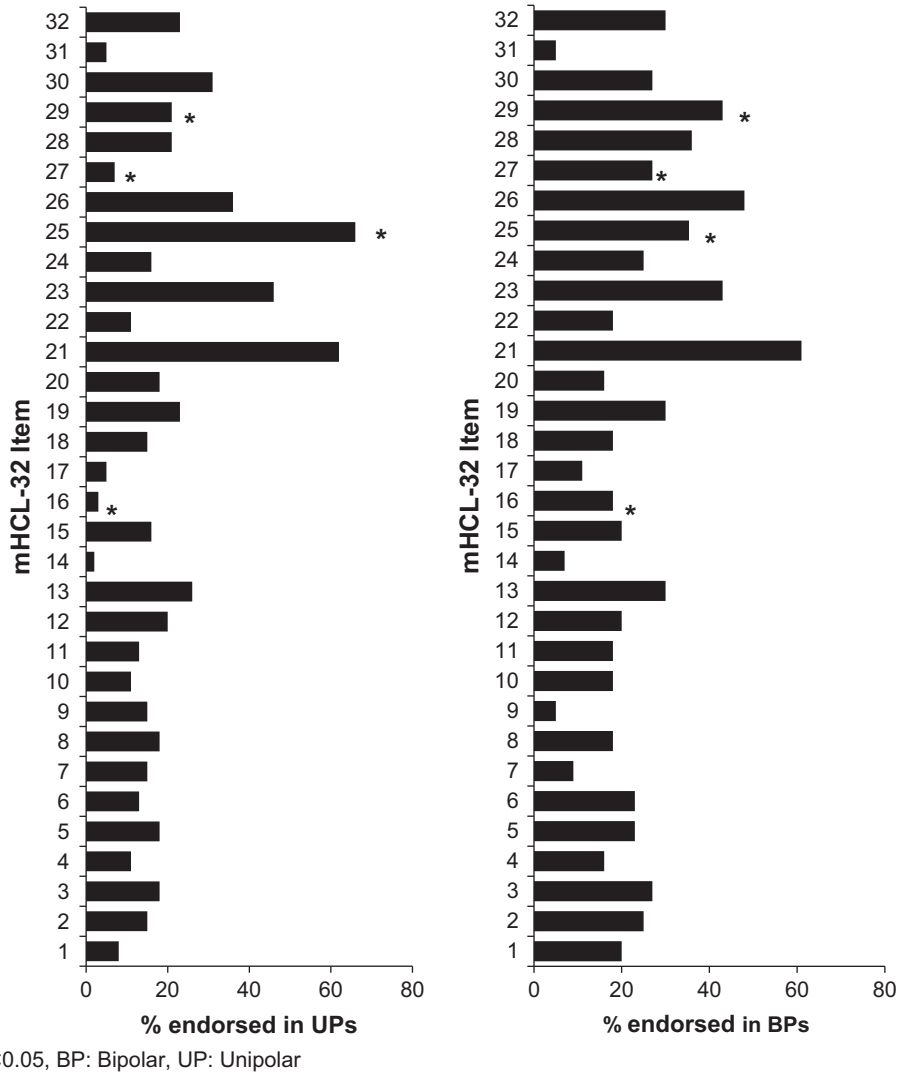

Fig. 1. Comparison of positive responses to each mHCL-32 item.*$p < 0.05$, BP: bipolar, UP: unipolar.

Table 2
Correlations of HAMD, YMRS, mHCL-32 and mHCL-32 subscores by diagnosis.

		mHCL-32	
		Active elevated	Irritable risk taking
YMRS	BP	$r=0.39$ $p=0.009$*	$r=0.03$ $p=0.825$
	UP	$r=0.21$ $p=0.092$	$r=0.29$ $p=0.021$*
HAMD	BP	$r=-0.24$ $p=0.135$	$r=0.37$ $p=0.017$*
	UP	$r=-0.37$ $p=0.004$*	$r=0.20$ $p=0.121$

mHCL-32: Modified Hypomania Check List, HAMD: Hamilton Depression Rating Scale,YMRS: Young Mania Rating Scale.
=Significant in bipolar subjects.
=Significant in unipolar subjects.
* $p<0.05$ Statistically significant

As reported in two large studies (Angst et al., 2011; Zimmermann et al., 2009),~40% of patient who met DSM-IV criteria for major depressive disorder also met criteria for subthreshold hypomania. This patient group also has been reported to have high rates of treatment resistance and treatment emergent switch (Akiskal et al., 1995; Hantouche et al., 2006; Dudeket al., 2010) as described in the international Bridge Study (Angst et al., 2011). Similar results have been obtained from studies on bipolar depression which have indicated that more than half of patients with bipolar depression had sub-syndromal manic symptoms and the use of antidepressants may have caused a manic switch in BP depressed patients who had (hypo)manic symptoms at baseline (Frye et al., 2009; Goldberg et al., 2007). Underestimation of manic (hypo) symptoms in depressive episode may cause inappropriate treatment selection, and worsening of the clinical course of depression. As such, developing a tool to detect these symptoms has merit.

There are several limitations of this study. First of all, this is a multinational study and patients were recruited from different countries, in both inpatient and outpatient academic and private practice settings; this may have introduced selection bias and heterogeneity with limited ability to generalize to less severe non-referral patient populations. Secondly, the sample size of the study was relatively small, with risk of type I error (i.e. false positive findings) or type II error (false negative findings). The p-values reported in the specific mHCL-32 items analysis were not corrected for multiple comparisons. The cross-sectional design does not allow making definite conclusions regarding the correlations found in this study. Lastly, we could not use the original HCL-32 cut off scores that were reported in the literature. The mHCL-32 was modified to assess current symptoms while HCL-32 is widely used to detect lifetime hypomanic symptoms.

Despite the limitations that are listed above, this is the first study aiming to develop a self-rating instrument for mixed depression. Modifying the HCL-32 to screen for manic (hypo) symptoms in a depressive episode may have utility in identifying mixed symptoms that may have differential endorsement in bipolar vs. unipolar depression or differentially parallel manic or depressive symptom severity. Considering the classification of mood disorders in DSM5 (i.e. the mixed features specifier in both unipolar and bipolar depression) the mHCL-32 may prove to be a useful scale for the clinicians to examine this new diagnostic category.

6. Conclusion

This study supports that more systematic attempts should be done to develop scales aimed at assessing mixed depression. Further studies, with larger sample sizes and change over time utilizing the mHCL-32 scale may provide clinicians a useful self-rating instrument to define complex mood states in patients with both unipolar and bipolar depression.

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Conflict of interest
Dr. Aydemir has received honoraria for speaker activities from Lundbeck, Astra Zeneca, Glaxo Smith Kline, Bristol Myers Squibb, for consultancy services from Servier, Pfizer and has received research support from Astra Zeneca.

Dr. Frye has been a consultant (unpaid) for Allergan, Merck, Myriad, Sanofi-Aventis, Sunovion, Takeda Global Research, Teva Pharmaceuticals, United Biosource Corporation, has received grant support from Myriad, Pfizer, National Alliance for Schizophrenia and Depression (NARSAD), National Institute of Mental Health (NIMH), National Institute of Alcohol Abuse and Alcoholism (NIAAA), Mayo Foundation and has received travel support from Chilean Society of Neurology, Psychiatry and Neurosurgery (Sociedad de Neurologia, Psiquiatria y Neurocirugia), Advanced Health Media, GlaxoSmithKline, Colombian Society of Neuropsychopharmacology, AstraZeneca, Bristol-Myers-Squib, Otsuka, Sanofi-Aventis.

Dr. Ozerdem has received honoraria from Astra Zeneca, BMS, Egis, GSK, Nobel, Pfizer, Servier and travel grants from Lundbeck, Nobel, Abdi İbrahim.

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The remaining authors have no potential conflicts to declare.

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