

# PSYCHIATRY ALERTS NOS

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## Substance Abuse and Bipolar Disorder Recovery

In a psychosocial-treatment trial, patients with bipolar disorder and a comorbid substance use disorder were significantly more likely to recover from depression within 1 year and to recover more rapidly than patients without a substance use disorder.

**Methods:** This study was a post-hoc analysis of data from a randomized treatment trial conducted within the large multicenter observational Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study. The analysis included patients who participated in a randomized trial, nested within STEP-BD, comparing 30 sessions of intensive psychotherapy (over 9 months) with a brief, psychoeducation-based collaborative care intervention. The aim of the analysis was to examine the effect of substance use disorders on the likelihood of recovery or time to recovery. Study subjects had bipolar I or II disorder and a current major depressive episode and were allowed to participate if they had a past alcohol or drug use or dependence disorder or a current disorder that did not require immediate treatment. Recovery—defined as  $\geq 8$  consecutive weeks with  $\leq 2$  DSM-IV depressive, manic, or hypomanic symptoms—was evaluated over  $\leq 1$  year of follow-up.

**Results:** Of the 270 study participants, about 55% had a lifetime substance use disorder and 17% had a current disorder; 13% had a current alcohol use disorder and 8% a current drug use disorder. In this sample, intensive psychotherapy was associated with a significantly greater likelihood of recovery (odds ratio,\* 1.66;  $p=0.04$ ) and a more rapid time to recovery (odds ratio, 1.42;  $p=0.03$ ) than collaborative care.

Patients with a current substance use disorder had a 2-fold higher likelihood of recovery than those without a current disorder ( $p=0.05$ ), as well as a more rapid onset of recovery ( $p=0.01$ ). Both drug and alcohol disorders, if current, were associated with improved recovery. Past substance use disorders were not associated with either outcome. Neither current nor past substance use disorders influenced patients' differential response to intensive psychotherapy versus collaborative therapy.

**Discussion:** This study is unique in allowing patients with concomitant substance use disorders to participate in a randomized treatment trial, and the results were contrary to the investigators'

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expectation that current substance use disorder would negatively impact recovery. Previous naturalistic observations of the STEP-BD cohort suggested that substance use disorders had a negative effect on recovery, or that they had no effect on recovery but increased the likelihood of a manic switch. A potential explanation for the present finding is a bias from the exclusion of patients with urgent substance problems.

Gold A, Peters A, Otto M, Sylvia L, et al: The impact of substance use disorders on recovery from bipolar depression: results from the Systematic Treatment Enhancement Program for Bipolar Disorder psychosocial treatment trial. *Australian & New Zealand Journal of Psychiatry* 2018; doi 10.1177/0004867418788172. From Boston University, MA; and other institutions. **STEP-BD is funded by the NIMH. Research described in this article was funded by the Dauten Family Center for Bipolar Treatment Innovation; and other sources. Seven of 11 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

\*See Reference Guide.

## Suicide Risk Factors in Bipolar Disorder

A Swedish population-based study identified a range of general, disorder-specific, and gender-specific risk factors for completed suicide in patients with bipolar disorder. Although this knowledge is valuable, suicide prevention efforts should not be based solely on risk factors.

**Methods:** The cohort consisted of patients enrolled in the Swedish National Quality Register for Bipolar Affective Disorder (BipolÄR) between 2004 and 2013. All patients with bipolar disorder who received treatment at psychiatric outpatient clinics in Sweden are offered registration. The register captures data collected by psychiatrists and staff in the course of clinical care and contains detailed information on sociodemographic factors, clinical history, family history, criminal convictions, and more. The study outcome was suicide, registered in Sweden's Cause of Death Register.

**Results:** The cohort consisted of 12,850 persons with bipolar disorder (62% women) who were followed for a median of 3.8 years. Within the cohort, there were 90 completed suicides, 55 in men and 35 in women. Identified risk factors for completed suicide included: male gender (hazard ratio [HR],\* 2.56); living alone (HR, 2.45); criminal conviction in the previous year (HR, 4.43); history of an affective episode in the previous year (HR, 2.39); depressive episode in the previous year (HR, 2.24); any comorbid psychiatric disorder (HR, 2.64); previous suicide attempt (HR, 4.1); inpatient psychiatric care in the previous year (HR, 2.79); and involuntary psychiatric hospitalization in the previous year (HR, 3.5). All associations were statistically significant ( $p < 0.01$  for all). Among comorbid psychiatric illnesses, risk of suicide was significantly increased with substance use (HR, 3.79), anxiety (HR, 1.91), and personality disorders (HR, 2.49), but not with eating disorders. Suicide was somewhat less frequent in patients with bipolar II disorder than type I, but the difference was not statistically significant. When data for men and women were analyzed separately, living alone, substance use disorder, involuntary commitment, and a recent affective episode were significant risk factors in men but not in women. Criminal conviction, comorbid personality disorder, and a recent depressive episode were significant predictors in women but not in men.

**Discussion:** It should be noted that as the registry included only Swedish patients, the results may not be generalizable to all populations. In addition, several other previously identified risk factors for suicide (e.g., early life adversity, family history of suicide, physical comorbidity, polarity of initial episode, total number of lifetime episodes, presence of psychotic features) were not captured in the registry.

Hansson C, Joas E, Pålsson E, Hawton K, et al: Risk factors for suicide in bipolar disorder: a cohort study of 12 850 patients. *Acta Psychiatrica Scandinavica* 2018; doi 10.1111/acps.12946. From the University of Gothenburg, Sweden; and other institutions. **Funded by the Swedish Research Council; and other sources. The authors declared no competing interests.**

\*See Reference Guide.

## Online Self-Help for Nonsuicidal Self-Injury

In a randomized trial of adults with nonsuicidal self-injury (NSSI), online interventions involving brief daily writing tasks reduced self-criticism, NSSI episodes, suicidal ideation, and depressive symptoms. The study's experimental treatment—Autobiographical Self-Enhancement Training (ASET)—had effects similar to another active control intervention and to a third control intervention that was intended to be inactive.

**Methods:** Participants were recruited from online forums related to self-injury and severe psychopathology. To enter the study, users were required to be aged  $\geq 18$  years and to have had  $\geq 2$  self-reported episodes of NSSI in the past month. The 3 randomly assigned treatments each involved a 5-minute daily writing assignment. The ASET assignment consisted of writing about something that made the participant feel good as a person. The active control, expressive writing, consisted of writing about something that bothered or concerned the individual. Journaling, the inactive control, consisted of simply recording the events of the day. Participants used anonymous email addresses and had no in-person contact with study personnel. They were emailed daily reminders and were paid for each completed assignment and weekly assessment. The primary study outcomes of self-reported episodes of NSSI and self-criticism, measured with the Self-Rating Scale, were evaluated online at the end of the 28-day interventions and again 4 weeks later.

**Results:** The sample consisted of 144 individuals (85% women), with a mean age of 26 years. The majority of patients had received psychiatric treatment, and about half were currently receiving treatment, 46% with medication. All patients completed  $\geq 1$  writing assignment, 77% completed  $>21$ , and 81% completed all follow-up assessments.

Regardless of treatment group, participants showed significant reductions in self-criticism ( $p < 0.001$ ) and in NSSI episodes ( $p = 0.02$ ). They also showed significant decreases in depression measured with the Beck Depression Inventory ( $p < 0.001$ ) and in suicidal ideation ( $p = 0.02$ ). Desire to discontinue NSSI, likelihood of future NSSI, suicidal plans, and suicidal behaviors all remained unchanged. There were few differences in outcomes between groups and they were not maintained at the 3-month follow-up, with the exception that ASET was associated with significantly fewer days of suicidal ideation compared with expressive writing ( $p = 0.048$ ). In a post-study evaluation, patients in the ASET group said that they found the writing assignments less enjoyable and more annoying than patients in either the expressive writing or journaling groups.

**Discussion:** All of the treatments provided clinical benefits and reduced episodes of NSSI. However, levels of self-criticism remained high, reductions did not persist after the end of treatment, and many outcomes were unaffected. The benefits of journaling were unexpected. All 3 writing interventions appear to warrant further investigation as highly scalable and easily disseminated treatments.

Hooley J, Fox K, Wang S, Kwashie A: Novel online daily diary interventions for nonsuicidal self-injury: a randomized controlled trial. *BMC Psychiatry* 2018; doi 10.1186/s12888-018-1840-6. From Harvard University, Cambridge, MA. Funded by the Eric M. Mindich Research Fund for the Foundations of Human Behavior. The authors declared no competing interests.

## Adjunctive VNS and Quality of Life in Depression

Vagus nerve stimulation is FDA approved as adjunctive treatment for resistant major depression. According to a longitudinal analysis of a registry of patients who received treatment for resistant depression, adjunctive VNS is also associated with clinically significant improvement in quality of life, persisting over 5 years of observation.

**Methods:** The 5-year registry enrolled patients with unipolar or bipolar depression, resistant to  $\geq 4$  antidepressant trials. All patients received treatment naturalistically with medication,

psychotherapy, and/or ECT or other neurostimulation. About half of the sample received adjunctive VNS. Follow-up evaluations were conducted every 3 months for the first year, and then at 6-month intervals. Quality of life was assessed with the Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form (Q-LES-Q-SF), a 14-item self-report instrument scored from 14 to 70, with higher scores indicating a better quality of life. Depression was assessed with the Montgomery-Asberg Depression Rating Scale (MADRS).

**Results:** The sample consisted of 271 patients receiving treatment as usual and 328 receiving adjunctive VNS. About one-fourth of patients had bipolar disorder; patients had a mean lifetime total of nearly 8 failed treatments and an average of nearly 2 suicide attempts. Average baseline Q-LES-Q scores were about 15% of the maximum possible.

Patients who received VNS had greater improvement in the Q-LES-Q than the control group, beginning 3 months after the start of treatment and lasting through the entire 5 years of observation. The effect of VNS was additive over the range of MADRS improvement, so that patients who received VNS had a mean Q-LES-Q improvement of 4 points compared with treatment-as-usual patients who experienced the same drop in the MADRS score. The effect was observed in patients with unipolar depression and in those with bipolar disorder, although the latter group was not large enough to demonstrate statistical significance. Previous research identified a Q-LES-Q increase of 11.89% as the minimal clinically important difference. In the present study, this level of improvement was reached by patients in the VNS group who had a  $\geq 34\%$  decrease from baseline in MADRS score, lower than the  $\geq 50\%$  decrease that typically defines treatment response. Patients in the treatment-as-usual group had a comparable Q-LES-Q improvement after achieving a  $\geq 56\%$  improvement in MADRS score. VNS was associated with an improved likelihood of achieving clinician-rated response, as measured by a Clinical Global Impression–Improvement rating of much or very much improved (odds ratio,\* 2.78). Of the individual domains measured by the Q-LES-Q, VNS was associated with greater improvements than control in mood, household activities, leisure activity, ability to function, overall well-being, social relationships, family relationships, and sex drive. Treatment-as-usual patients had better economic status; the groups had similar results for the remaining 4 domains.

**Discussion:** These findings are potentially important because patients in this highly refractory group are unlikely to experience response to additional medications. The positive results of the present study suggest that randomized controlled trials to evaluate quality-of-life effects of adjunctive VNS in this difficult-to-treat population are warranted.

Conway C, Kumar A, Xiong W, Bunker M, et al: Chronic vagus nerve stimulation significantly improves quality of life in treatment-resistant major depression. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.18m12178. From Washington University School of Medicine in St Louis, MO; LivaNova PLC (Cyberonics, Inc.), Houston, TX; and other institutions. **Funded by Cyberonics, Inc. Five of 6 study authors disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

\*See Reference Guide.

## Biological Aging in Depression

A Dutch cohort study found epigenetic aging, an indicator of biological aging, was advanced in individuals with depression compared with a group of healthy subjects. The accelerated biological aging in these patients may contribute to the increased risk for mortality and aging-related diseases observed in patients with depression.

**Methods:** DNA methylation provides a marker of biological age (DNAm age) that can be compared with an individual's biological age. The present study compared DNAm age estimates in participants in the Netherlands Study of Depression and Anxiety longitudinal cohort study. For this analysis, the investigators selected a subset of the cohort who had current or lifetime major depressive disorder, with a score of  $\geq 14$  on the Inventory of Depressive

Symptomatology (IDS), and a control group with current IDS scores <14 and no lifetime psychiatric disorders. DNA methylation was assessed using blood samples, and age estimation was based on chronological ages of the full study group (n=811) and of only control subjects (n=319). The DNAm age analysis was replicated in postmortem brain samples from 4 different U.S. and European brain banks.

**Results:** The mean chronological age of both groups was 41.5 years. According to epigenetic aging estimates, patients with depression were an average of 0.64 years, or 7.7 months, older than controls (p=0.008) after adjustment for a wide array of covariates. Greater epigenetic aging was associated with higher scores on the IDS in the overall sample (p=0.001). Epigenetic aging was also associated with higher scores on a Dutch structured inventory of childhood trauma (p=0.001). Depression severity was also correlated with childhood trauma (p<0.001), which makes it difficult to discern which of these 2 factors accounts for increased epigenetic aging. Aging was not associated with clinical characteristics of depression, including age at onset, illness duration, or medication use. These findings were replicated in postmortem brain samples from 74 persons with depression and 67 controls, matched for chronological age and gender. The depression group was estimated to be on average 1.11 years older by DNAm than the control group (p=0.03).

**Discussion:** Epigenetic aging has been linked with many physical illnesses and behavioral risk factors, but associations with life stressors and mental illnesses such as schizophrenia have been mixed. The present observations indicate that advanced aging is present in both the blood and brain of patients with depression, suggesting that at least some processes that affect epigenetic aging are active in both tissues. Because the study was cross-sectional, it was not possible to discover whether accelerated epigenetic aging occurs before adulthood, possibly as a consequence of childhood trauma, or whether greater epigenetic aging occurs throughout life.

Han L, Aghajani M, Clark S, Chan R, et al: Epigenetic aging in major depressive disorder. *American Journal of Psychiatry* 2018;175 (August):774–782. doi 10.1176/appi.ajp.2018.17060595. From the VU University Medical Center, the Netherlands; and other institutions. **Funded by the Netherlands Organization for Health Research and Development; the NIMH; and other sources. One of 15 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

## Smartphone Apps for Mental Health

Use of mental health smartphone apps significantly improved well-being in a nonclinical population. Two of the 3 evaluated apps were associated with reductions in depressive symptoms, but no app reduced anxiety symptoms.

**Background:** Mental health apps may be most useful in preventive and stepped-care approaches to emotional problems. However, previous studies and meta-analyses have relied on clinical samples, programs that require clinician-delivered feedback, and programs that are not available to the public. The present study is notable for being conducted in a nonclinical population using generally available programs, for examining effects on positive well-being, and for exploring mechanisms that may mediate the effects of the apps.

**Methods:** The study compared the effects of MoodPrism, MoodMission, and MoodKit, all self-guided CBT-based apps that use different therapeutic techniques. Participants were recruited using social media, and were then randomly assigned to 1 of the apps or to a wait-list control condition. The 3 apps were available from the Australian iOS and Android app stores, either without cost or using free access provided by the study. Efficacy outcomes were: depression symptoms, measured with the Patient Health Questionnaire-9 (PHQ-9); anxiety symptoms, measured with the 7-item Generalized Anxiety Disorder Scale (GAD-7); and mental wellbeing, measured with the Warwick-Edinburgh Mental Well-being Scale (WEMWBS). Outcomes were assessed using these measures via email link, with the final assessment after 30 days.

The apps include features that may increase emotional self-awareness (particularly MoodPrism and MoodKit), coping self-efficacy (particularly MoodMission and MoodKit), and mental health literacy (all 3 programs). Each of these 3 intermediate outcomes was examined as a potential mediator of the ultimate treatment effects.

**Results:** Study participants (n=226) had a mean age of 34 years, 81% were women, and 141 completed the 30-day assessment. At baseline, 55% of subjects had PHQ-9 scores indicating a likely depression diagnosis, and 36% had GAD-7 scores indicating a likely anxiety disorder.

Compared with the waitlist control group, participants who used any active intervention showed improvement in mental well-being, and users of MoodKit and MoodMission had reductions in depressive symptoms. (See table.)

All active treatments were associated with increases in coping self-efficacy, which was shown to mediate the positive effects of MoodKit and MoodMission. Changes in emotional self-awareness and mental health literacy were small and did not mediate the mental health outcomes.

Effects of 3 smartphone apps on depression, anxiety, and mental wellbeing					
Outcome	Intervention	Change from baseline		Difference from control	
		Effect size <sup>†</sup>	Significance	Effect size <sup>†</sup>	Significance
Depression (PHQ-9)	Control	0.069	p<0.05	—	—
	MoodKit	0.341	p<0.001	0.035	p<0.05
	MoodPrism	0.237	p<0.001	0.007	NS
	MoodMission	0.318	p<0.001	0.038	p<0.05
Anxiety (GAD-7)	Control	0.020	NS	—	—
	MoodKit	0.153	p<0.01	0.017	NS
	MoodPrism	0.136	p<0.01	0.009	NS
	MoodMission	0.146	p<0.01	0.017	NS
Well-being (WEMWBS)	Control	0.066	p<0.05	—	—
	MoodKit	0.438	p<0.001	0.074	p<0.01
	MoodPrism	0.392	p<0.001	0.037	p<0.05
	MoodMission	0.558	p<0.001	0.089	p<0.001

<sup>†</sup>Using the partial eta-squared statistic; see Reference Guide

**Study Rating\*—15 (88%):** This study met most criteria for a randomized controlled trial; however, the source of funding was not included in the report.

Bakker D, Kazantzis N, Rickwood D, Rickard N: A randomized controlled trial of three smartphone apps for enhancing public mental health. *Behaviour Research and Therapy* 2018;109:75–83. doi 10.1016/j.brat.2018.08.003. From Monash University, Australia; and other institutions. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

\*See Reference Guide.

## Reference Guide

**Effect Size (Partial Eta-Squared):** The effect size represents the amount of change in outcome that can be attributed to treatment, when using the partial eta squared statistic, 0.01 indicates a small effect, 0.06 a medium effect, and 0.14 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

**Hazard Ratio:** A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

**Odds Ratio:** A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

**Study Rating:** A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ).

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