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3 **The potential use of histone deacetylase inhibitors in the treatment of depression**  
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4 **Abstract**  
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6 Numerous preclinical studies demonstrate that changes in gene expression in the brain  
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8 occur in animal models of depression using exposure to stress, such as social defeat and  
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10 leaned helplessness, and that repeated administration of antidepressants ameliorates  
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12 these stress-induced changes in gene expression. These findings suggest that alteration  
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14 in gene transcription in the central nervous system in response to stress plays an  
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16 important role in the pathophysiology of depression. Recent advances in epigenetics  
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18 have led to the realization that chromatin remodeling mediated by histone deacetylase  
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20 (HDAC) is closely involved in the regulation of gene transcription. In this context, we  
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22 first review several preclinical studies demonstrating the antidepressant-like efficacy of  
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24 HDAC inhibitors. We then suggest the efficacy of HDAC inhibitors in  
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26 treatment-resistant depression based on the mechanism of action of HDAC. Finally, we  
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28 discuss the possibility of using HDAC inhibitors in patients with treatment-resistant  
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30 depression.  
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5 **Introduction**  
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8 Major depression was ranked first among 10 leading diseases with respect to global  
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10 disease burden in high-income countries in 2001 as indicated by a systematic analyses  
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12 of population health data, and it accounted for the third-highest number of  
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14 disability-adjusted life years (Lopez et al., 2006). Although different types of  
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16 antidepressants including selective serotonin reuptake inhibitors (SSRIs), serotonin  
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18 noradrenaline reuptake inhibitors (SNRIs), bupropion, and mirtazapine, have been  
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20 developed and used clinically, a certain percentage of patients with depression do not  
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22 show an adequate response to these newer antidepressants or to tricyclic  
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24 antidepressants.  
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37 Results from the Sequenced Treatment Alternatives to Review Depression  
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39 (STAR\*D) study demonstrated that almost 35% of 3671 patients with nonpsychotic  
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41 major depressive disorder did not achieve remission, despite undergoing 1 to 4  
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43 successive treatment steps during which 6 different types of antidepressants (SSRI,  
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45 SNRI, tricyclic antidepressant, bupropion, mirtazapine, and monoamine amine oxidase  
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47 inhibitor) were administered (Rush et al. , 2006). Similarly, the Combining Medications  
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49 to Enhance Depression Outcomes (CO-MED) study showed that the remission rate of a  
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59 12-week combination treatment with the 2 different types of antidepressants including  
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3 bupropion, mirtazapine, citalopram, and venlafaxine, was approximately 40% among  
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6 patients with major depression (Rush et al., 2011). Given the limited efficacy of  
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9 antidepressants, the use of aripiprazol to augment antidepressant therapy is approved by  
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12 the U.S. Food and Drug Administration (FDA) for patients with antidepressant-resistant  
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15 depression. In addition, electroconvulsive treatment is often selected in the treatment of  
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18 drug-resistant depression in Japan. Given that there exists such a large percentage of  
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21 depressed patients who are drug-resistant, a new class of antidepressants with  
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24 mechanisms distinct from the regulation of monoaminergic signal transduction is  
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27 required.  
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32 Preclinical studies on the pathophysiology of depression suggest that changes in  
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35 gene expression, such as brain-derived neurotrophic factor (BDNF) (Duman et al.,  
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38 1997; Nestler 2002), glial cell line-derived neurotrophic factor (GDNF) (Hisaoka et al.,  
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41 2001; Uchida et al., 2011), and vascular endothelial growth factor (VEGF) (Greene et  
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44 al., 2009), in the brain may be closely involved in the development of depression. With  
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47 respect to gene transcription, recent epigenetic studies show that the regulation of  
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50 chromatin structure by both histone modifications and DNA methylation plays an  
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53 important role (Ashraf et al., 1998; Lieb and Clarke, 2005; Verdin and Ott, 2014). In  
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56 fact, while valproic acid (VPA), a histone deacetylase inhibitor, has a long history of use  
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3 in the treatment of bipolar disorder as a mood stabilizer (Phiel et al., 2001), VPA was  
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6 reported to increase the activity of BDNF promoter IV and the level of exon  
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9 IV-containing BDNF mRNA (Yasuda et al., 2009). In this paper, we review the efficacy  
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12 of HDAC inhibitors as antidepressants based on evidence from the rodent studies, and  
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16 discuss the clinical potential of HDAC inhibitors for the treatment of depression.  
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## 22 **Transcriptional regulation by histone deacetylase inhibitors**

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25 Numerous preclinical studies postulate that the effect of antidepressants requires  
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28 alterations in central signal transduction mediated by gene transcription (Myers and  
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31 Davis, 2002). Transcription is regulated by the concerted action of transcription factors  
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34 and cofactors that modify and remodel the structure of chromatin (Holliday, 2006). Thus,  
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37 a clear understanding of the epigenetic mechanisms of depressive symptoms and  
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40 associated alterations in gene expression may provide opportunities for the development  
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43 of novel therapies. Histone acetylation, which alters the compact chromatin structure  
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46 and changes the accessibility of DNA to transcriptional factor proteins, is emerging as a  
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49 fundamental mechanism for regulating gene expression (Goldberg et al., 2007,  
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52 Kurdistani and Grunstein, 2003).  
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57 Histone acetylation is regulated by the opposing activities of histone  
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3 acetyltransferases (HATs) and HDACs (Kramer et al. , 2001). These enzymes maintain  
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6 the equilibrium of acetyl groups added to or from histone protein, mainly H3 and H4.  
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9 Activation of HAT facilitates the binding of acetyl groups to histone protein and  
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12 subsequently increases the acetylation levels of histone in the nucleus. In contrast,  
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15 activation of HDAC catalyzes the removal of acetyl groups from histone protein, and  
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18 subsequently decreases histone acetylation. In this context, administration of an HDAC  
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21 inhibitor prevents the decrease in histone acetylation, leading to sustained activation of  
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26 gene transcription.

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29 To date, 18 different HDACs are known in humans, and these enzymes are  
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32 classified into 2 families and 4 classes (Khochbin et al., 2001). The 2 families are the  
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35 classical zinc-dependent family and the silent information regulator 2-related protein  
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38 (SIRT) family, which are nicotinamide-adenine-dinucleotide (NAD)-dependent. The  
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41 classical HDACs are very similar in structure and divided into 4 classes: class I  
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44 (HDACs 1, 2, 3, 8), class IIa (HDACs 4, 5, 7, 9), class IIb (HDACs 6, 10), and class IV  
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47 (HDAC11) (Walkinshaw and Yang XJ, 2008). The class I HDACs are found mostly  
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50 within the nucleus and are expressed ubiquitously, whereas class II members shuttle  
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53 between the nucleus and cytoplasm (Gibson and Murphy 2010), with the exception of  
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56 HDAC6, which are located only in the cytoplasm. Class IV HDAC, HDAC11, is  
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3 structurally different from class I and class II HDACs. On the other hand, the class III  
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6 SIRT gene family consists of 7 isoforms in human (Grozinger et al., 2001). SIRTs 1, 2, 6,  
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9 and 7 are found in the nucleus, whereas SIRTs 3, 4, and 5 are found in the mitochondria  
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12 (Han, 2009; Michishita et al., 2005). In addition, the HDACs are expressed in a cell and  
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15 tissue-specific manner. For instances, class I, II, and IV HDACs are expressed primarily  
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18 in neurons (Broide et al., 2007). While the expression levels of HDACs 2, 3, 4, 5, 11 are  
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21 relatively high in oligodendrocytes (Gräff, and Tsai, 2013), the expression of most  
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25 SIRTs is higher in fetal brain compared to adult brain (Michishita et al., 2005).  
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28 HDAC inhibitors are divided into groups based on their chemical structure,  
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30 including hydroxamic acids, carboxylic acids, aminobenzamides, cyclic peptides,  
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32 epoxyketones, and hybrid molecules (Grayson et al., 2010; West and Johnstone, 2014).  
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35 Extensive studies examining the specific target enzymes of HDAC inhibitors have been  
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38 undertaken. For example, vorinostat (SAHA), a hypoxamate-based inhibitor, acts on  
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41 HDAC1, 2, 3, 4, and 8; MS-275, a bezamide-based inhibitors, acts on HDAC 1, 2, 3,  
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44 and 9. Romidepsin, a cyclic peptide-based inhibitors, acts on HDAC1 and 2. The  
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47 development of isozyme-selective HDAC inhibitors may be an important mean by  
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50 which to achieve enhanced therapeutic efficacy and reduced toxicity.  
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57 If global reduction in gene expression in certain brain regions, such as the  
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3 hippocampus and prefrontal cortex, in response to stress is involved in the  
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6 pathophysiology of depression, then chronic but not acute treatment with an HDAC  
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9 inhibitor could antagonize the decrease in gene transcription induced by stress, and  
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12 consequently exert antidepressant-like efficacy. However, intra-nucleus accumbens  
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15 (NAc) administration of an HDAC inhibitor has also been reported to produce  
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18 antidepressant-like effects in mice subjected to chronic social defeat stress (Covington  
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21 et al., 2009). Therefore, both systemic as well as regional administration of HDAC  
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24 inhibitors exhibits an antidepressant-like efficacy.  
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### 32 **Epigenetic discoveries leading to new treatments for major depression**

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35 While numerous rodent studies have revealed alterations in gene expression  
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38 profiles in the brain in response to stress exposure, it is well recognized that chronic  
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41 administration of antidepressant drugs leads to alterations in gene expression profiles,  
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44 and consequently ameliorates the aberrant gene expression that follows stress exposure.  
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47 Based on these findings, it is conceivable that histone modifications are only one of the  
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50 key factors involved in the pathophysiology of major depression. Current  
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53 pharmacotherapies for depression using SSRIs and/or SNRIs have substantial  
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56 limitations. For example, there is a significant delay between the onset of  
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3 pharmacological action and achievement of a therapeutic response (Rosenzweig-Lipson  
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6 et al., 2007). In addition, even with appropriate pharmacological treatments, less than  
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9 50% of patients with depression achieve full remission (Little, 2009). It is therefore  
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12 imperative to develop a new epigenetic drug with a faster onset and greater efficacy in  
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16 the treatment of major depression.  
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19           Several recent rodent studies (Bilang-Bleuel et al., 2005, Chandramohan et al.,  
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22 2008, Covington et al., 2009, Covington et al., 2011, Ferland and Schrader, 2011,  
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25 Fuchikami et al., 2009, Hollis et al., 2010, Lin et al., 2012, Renthal et al., 2007,  
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28 Tsankova et al., 2006, Uchida et al., 2011) have demonstrated that stress exposure and  
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31 antidepressants affect histone modifications (Table 1). For example, Tsankova and  
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34 colleagues (2006) showed that down-regulation of HDAC5 was associated with the  
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37 antidepressant efficacy of imipramine in a social defeat stress paradigm. Sodium  
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40 butyrate (SB) alone or in combination with fluoxetine was shown to have  
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43 antidepressant-like effects in the tail suspension test (TST) in mice (Schroeder et al.,  
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46 2007). Similarly, we recently demonstrated that repeated administration of SB  
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49 significantly reduced immobility on the forced swimming test (FST) and the TST  
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52 (Yamawaki et al., 2012). These findings suggest that the activity of HDACs might be  
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57 involved in the therapeutic actions of antidepressants.  
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3 A series of studies conducted by Nestler and colleagues (Covington et al., 2009,  
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6 Renthall et al., 2007) revealed that the levels of acetylated histone H3 were persistently  
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9 increased in the NAc after chronic social defeat stress, and this effect was accompanied  
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12 by decreased levels of HDAC2 in the NAc. Infusion of MS-275 (a specific class I  
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15 HDAC inhibitor) into the NAc after stress had antidepressant-like effects in several  
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18 behavioral tests. Moreover, global patterns of gene expression in the NAc after MS-275  
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21 infusion showed fluoxetine-like gene expression profiles. Uchida and colleagues (2011)  
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24 reported that chronic ultra-mild stress enhanced the mRNA levels of HDAC2 in the  
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27 NAc of BALB/c mice, and the enhancement was reversed by infusion of imipramine.  
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30 Furthermore, BALB/c mice overexpressing dominant-negative HDAC2 in the NAc  
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33 showed increased social interaction times and greater sucrose preference compared with  
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36 controls. Renthall and co-workers (2007) found that chronic social defeat stress  
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39 down-regulated HDAC5 mRNA in the NAc, whereas chronic treatment with  
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42 imipramine alleviated the down-regulation of HDAC5 mRNA. Moreover,  
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45 HDAC5-knockout mice exhibited more severe social avoidance after chronic social  
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48 defeat stress as compared with controls. In contrast to the findings in the NAc, chronic  
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51 social defeat stress caused a persistent decrease in the levels of acetylated histone H3 in  
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54 the hippocampus (Covington et al., 2011). This change was reversed by chronic  
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3 systemic administration of fluoxetine and intra-hippocampal infusion of MS-275.  
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6 Infusion of MS-275 into the hippocampus increased sucrose preference after chronic  
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9 social defeat stress, but it did not ameliorate stress-induced social avoidance. Taken  
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12 together, these findings support the antidepressant potential of HDAC inhibitors and  
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14  
15 provide new insight into the epigenetic mechanisms of depression and antidepressants.  
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19 As shown in Table 1, the NAc and hippocampus are the 2 most studied brain  
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22 regions in general; however, a limited number of studies of the amygdala (Covington et  
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25 al., 2011, Renthal et al., 2007) and prefrontal cortex (Lin et al., 2012) have been  
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28 published. For example, Lin and colleagues recently demonstrated that chronic infusion  
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31 of MS-275 into the ventrolateral orbital cortex (VLO) significantly reduced immobility  
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34 time in the FST and TST compared with controls, similar to the effects of systemic  
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37 administration of fluoxetine, and these antidepressant-like effects of MS-275 were  
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40 associated with an increase in H3 acetylation, CREB, and BDNF in the VLO (Lin et al.,  
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43 2012). It has been suggested that the orbitofrontal cortex might be involved in the  
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46 pathogenesis of depression (Drevets, 2007); therefore, further studies are needed to  
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49 elucidate the involvement of histone modification in this brain region. A summary of the  
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52 **genes and brain regions involved in the antidepressant-like efficacy of HDAC inhibitors**  
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55 **is presented in Table 2.**  
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3 It would also be helpful to utilize reliable indicators of drug efficacy, if  
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6 suitable biomarkers can be identified in peripheral blood. One study reported that  
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9 mRNA levels of HDAC5 and CREB were significantly higher in drug-free depressive  
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12 patients than in controls, and the higher mRNA levels returned to control levels after  
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15 treatment with paroxetine (Iga et al., 2007). Another recent study observed that in  
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18 patients with major depressive disorder, the expression of HDAC2 and HDAC5 was  
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21 enhanced in a depressive state but not in a remissive state (Hobara et al., 2010). These  
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24 findings suggest that altered expression of HDAC mRNA in peripheral blood is  
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27 promising as a biological marker.  
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32 If chromatin condensation occurs as a result of stress exposure through the  
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35 aberrant expression and activity of HDACs, then the binding of transcription factors,  
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38 such as phospho-CREB, to their binding sites may be impeded even though the levels of  
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41 transcription factors are increased by chronic antidepressant treatment. If the  
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44 accessibility of transcription factors to their binding sites is decreased due to chromatin  
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47 condensation in major depression, the efficacy of antidepressants may fail to be exerted.  
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50 In this context, the combined administration of an antidepressant and an HDAC  
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53 inhibitor could be helpful in the treatment of antidepressant-resistant patients with major  
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56 depression (Figure 1).  
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6 **Clinical potential of HDAC inhibitors for the treatment of depression**  
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8           To date, no clinical trials have been conducted to evaluate HDAC inhibitors for  
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10 the treatment of depression; therefore the clinical potential for such therapy in the  
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12 treatment of patients with depression remains unknown. Based on the results of the  
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14 clinical trial of vorinostat and romidepsin on refractory cutaneous and peripheral T cell  
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16 lymphoma, the U.S. FDA recently approved these HDAC inhibitors for clinical use. In  
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18 addition, the efficacy and safety of sodium butyrate, and MS-275 have been examined  
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20 for the treatment of cancer, although the possibility of clinical use of these HDAC  
21  
22 inhibitors remains controversial for treatment of cancer. Vorinostat was the first HDAC  
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24 inhibitor drug to be approved for clinical use by the FDA for the treatment of refractory  
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26 cutaneous T-cell lymphoma. In line with the efficacy results observed with HDAC  
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28 inhibitors in rodent models of depression, our previous study demonstrated that  
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30 administration of vorinostat in conjunction with extinction training of conditioned fear  
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32 markedly ameliorated impaired fear memory extinction in an animal model of  
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34 posttraumatic stress disorder (PTSD) (Fujita et al., 2012, Vecsey et al., 2007). In studies  
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36 of HDAC inhibitors, a key difference observed between animal models of depression  
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38 and PTSD is the duration of HDAC inhibitor administration required to produce an  
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40 effect; i.e., in our rat model of PTSD a single administration of vorinostat was effective  
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3 in improving impaired fear extinction. In contrast, in animal studies of depression,  
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6 HDAC inhibitors had to be administered chronically to produce an antidepressant-like  
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9 effect, suggesting that long-term administration may be needed in the clinical treatment  
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12 of depression. The clinical potential of vorinostat is limited by the drug's adverse  
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15 effects. The most common clinical adverse events of any grade are diarrhea (52%),  
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18 fatigue (52%), nausea (41%), and anorexia (24%) (Mann et al., 2007). Therefore, in the  
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21 treatment of depression it may be problematic to use vorinostat chronically as it is in  
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25 cancer therapy, but not acutely.  
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### 31 **Summary and implications**

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35 Almost all studies examining the antidepressant-like efficacy of HDAC inhibitors in  
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38 rodent models of depression support the clinical potential of using HDAC inhibitors for  
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41 the treatment of depression. Some studies have shown that administration of HDAC  
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44 inhibitors augments the effect of antidepressants, suggesting that a combination of  
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47 antidepressants and HDAC inhibitors could serve as a valuable new treatment for  
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50 patients with antidepressant-resistant depression. Although the precise mechanism of  
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53 the antidepressant effects of HDAC inhibitors is unknown, it is conceivable that  
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57 changes in chromatin structure, such as the initiation of a loose chromatin condition, by  
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3 HDAC inhibitors, may facilitate gene transcription induced by antidepressants. At the  
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6 present time, vorinostat and romidepsin are the only FDA-approved HDAC inhibitors,  
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9 both for the treatment of hematologic cancer, but no drugs in this class have been  
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12 approved for the treatment of depression. Clinical trial evaluations of HDAC inhibitors  
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15 for the treatment of depression, especially antidepressant-resistant depression, are  
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18 warranted. The adverse event profiles demonstrated in clinical trials of vorinostat and  
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21 romidepsin for the treatment of cancer indicate that the use of HDACs for the treatment  
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24 of depression may be feasible. Since newer HDAC inhibitors with less toxicity have  
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27 been developed for use in cancer therapy, these drugs may also hold promise for the  
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30 pharmacotherapy of antidepressant-resistant depression.  
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3 **Figure Caption**  
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6 **Figure 1.** If levels of histone acetylation were low during administration of  
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8 antidepressants, transcription factors, such as phospho-CREB and AP-1, hardly bind to  
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10 their specific binding sites, and subsequently the transcription rates of various genes are  
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12 not induced. In contrast, coadministration of antidepressant and HDAC inhibitor can  
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14 sustain increased levels of histone acetylation, and facilitate the  
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16 antidepressant-stimulated increase in the transcription rates of various genes. Therefore,  
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18 it is conceivable that coadministration may enhance the efficacy of antidepressants.  
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20 AP-1: activator protein 1; BS; binding site; CRE, cAMP response element; CREB,  
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22 cAMP response element binding protein; p-CREB; phospho-CREB.  
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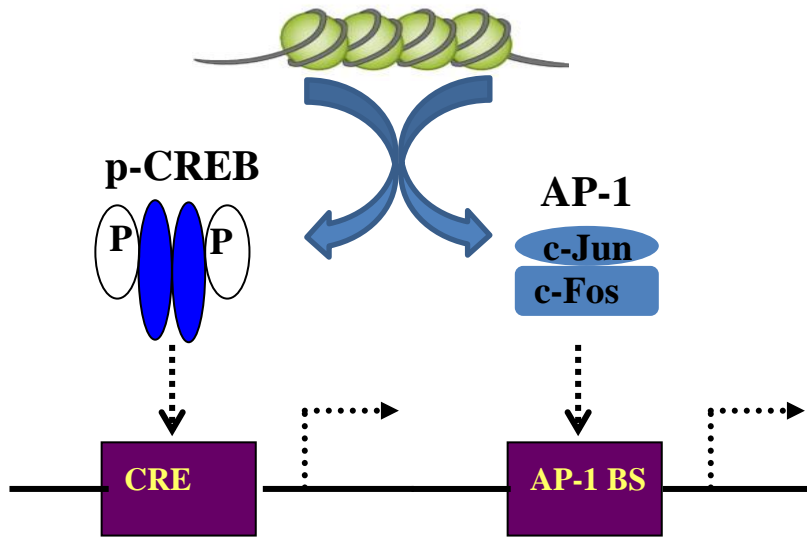
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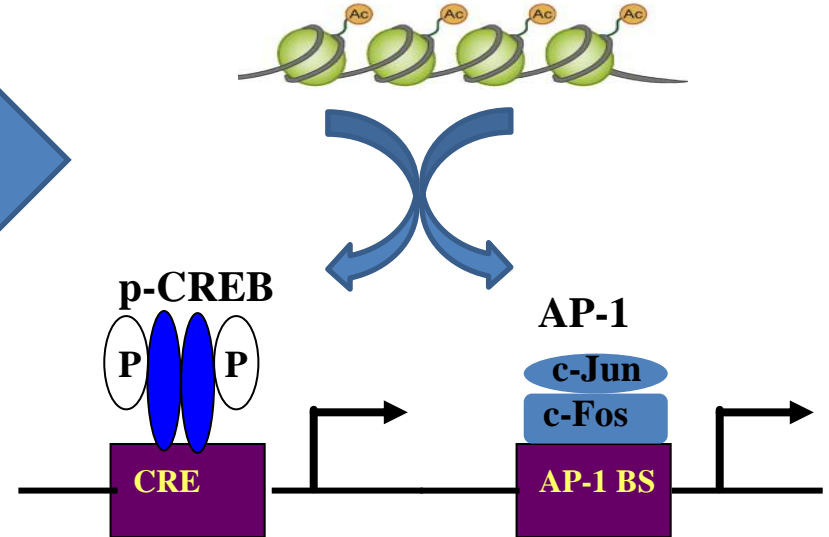
Administration of antidepressant

Hypoacetylation status



Coadministration of antidepressant and HDAC inhibitor

Hyperacetylation status



**Table 1. Regulation of histone modification and HDAC expression by stress and antidepressants**

<i>Treatment</i>	<i>Effect</i>	<i>Reference</i>
Social defeat stress	Increase in acetylated H3 in the NAc Decrease in HDAC2 in the NAc	Covington et al. (2009)
Social defeat stress + imipramine	Decrease in HDAC5 in the NAc Imipramine reverses the HDAC5 expression	Renthal et al. (2007)
Chronic ultra-mild stress + imipramine	Increase in HDAC2 in the NAc Imipramine reverses the HDAC2 expression	Uchida et al. (2011)
Forced swim stress	Increase in phospho-acetylated H3 in the Hp	Chandramohan et al. (2008)
Forced swim stress	Increase in phospho-acetylated H3 in the Hp	Bilang-Bleuel et al. (2005)
Predator stress	Increase in phospho-acetylated H3 in the Hp	Bilang-Bleuel et al. (2005)
Social defeat stress	Increase in acetylated H3 in the Hp No change in acetylated H4 in the Hp	Hollis et al. (2010)
Chronic variable stress	Decrease in acetylated H4 in the Hp Decrease in phospho-acetylated H3 in the Hp	Ferland et al. (2011)
Social defeat stress + imipramine	Decrease in acetylated H3 in the Hp Imipramine reverses this change	Covington et al. (2011)
Single immobilization stress	Decrease in acetylated H3 at the promoters of exon 1,4,6 (BDNF) in the Hp	Fuchikami et al. (2009)
Social defeat stress + imipramine	Increase in HDAC5 in the Hp Imipramine reverses this change	Tsankove et al. (2006)

NAc, nucleus accumbens; Hp, hippocampus.

**Table 2. Involvement of brain regions and genes in the antidepressant-like effect of HDAC inhibitors**

<b>Study</b>	<b>HDAC Inhibitor</b>	<b>Brain Region</b>	<b>Gene</b>
<b>Lin et al. (2012)</b>	<b>MS-275</b>	<b>Ventrolateral Orbital Cortex</b>	<b>CREB, BDNF</b>
<b>Han et al. (2014)</b>	<b>Sodium Butyrate</b>	<b>Hippocampus</b>	<b>BDNF (after CRS)</b>
<b>Schroeder et al. (2007)</b>	<b>Sodium Butyrate</b>	<b>Frontal Cortex</b>	<b>BDNF</b>
<b>Uchida et al. (2011)</b>	<b>Vorinostat</b>	<b>Ventral Striatum</b>	<b>GDNF</b>
<b>Schmauss (2015)</b>	<b>Trichostatine A</b>	<b>Forebrain Neocortex</b>	<b>BDNF</b>
<b>Yamawaki et al. (2012)</b>	<b>Sodium Butyrate</b>	<b>Hippocampus</b>	<b>Transthyretin, 5-HT2A</b>
<b>Covington et al. (2009)</b>	<b>MS-275</b>	<b>Nucleus Accumbens</b>	<b>Cort, Gja5, Adra1a (after CSD)</b>

**CRS: chronic restraint stress, CSD: chronic social defeat**

**CREB: cAMP response element binding protein, 5-HT2A: serotonin 2A receptor, Cort: cortistatin,**

**Gja5: gap junction protein  $\alpha$ 5, Adra1a: adrenergic  $\alpha$ 1A receptor**