

# Dengue and Psychiatry: Manifestations, Mechanisms, and Management Options

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## ABSTRACT

Dengue is an arboviral infection endemic in tropical countries. Neurological sequelae to dengue infection are not uncommon, and psychiatric manifestations are increasingly reported. This narrative review aims to present the varied manifestations, postulated mechanisms, and the available treatment options for psychiatric morbidity associated with dengue. The evidence available from eight observational studies is summarized in this review. Depression and anxiety are noted to be prevalent during both the acute and convalescent stages of the infection. The presence of encephalopathy and other neurological conditions is not a prerequisite for developing psychiatric disorders. However, treatment options to manage such psychiatric manifestations were not specified in the observational studies. Anecdotal evidence from case reports is outlined. Special attention is paid to the role of epigenetic modifications following dengue infections and the role of histone deacetylase inhibitors in the management. DNA methylation inhibitors such as valproic acid play a significant role in reversing stress-, viral-, or drug-induced epigenetic modifications.

**Keywords:** Dengue, psychiatry, depression, valproate, histone deacetylase, quetiapine

Dengue is a viral illness caused by a single-stranded ribonucleic acid (RNA) virus belonging to the Flaviviridae family with four different dengue serotypes (DENV 1–4). It is transmitted by infected *Aedes* mosquitoes. It is a global epidemic with an incidence of around 96 million apparent infections per year<sup>1</sup> and a significant social and economic burden.<sup>2,3</sup> India alone contributes more than one-third of such apparent clinical infections.<sup>1</sup> Dengue is endemic in tropical countries, and the incidence of the infection has been progressively increasing through the last two decades.<sup>4,5</sup> The illness usually has an abrupt onset, with a course characterized by fever, critical, and convalescence phases.<sup>5</sup> The World Health Organization classifies the illness into two groups: uncomplicated and severe dengue.<sup>6</sup> In the Indian context, severe dengue has been estimated to be 35% of all dengue cases, with a mortality rate of 2% to 3%.<sup>7</sup> All four serotypes are prevalent in India.<sup>8</sup>

The critical period marks the essential phase of the severity of the illness that may ultimately lead to hepatic, cardiac, and neurological consequences. To date, there are no approved antiviral drugs available to treat dengue, and the management is mostly symptomatic and supportive.<sup>6</sup>

Dengue's neurological involvement is increasingly recognized but not well understood. DENV-2 and DENV-3 serotypes are reported to be associated with neurological manifestations.<sup>9</sup> Although the studies on incidence rates of neurological sequelae secondary to dengue infection are limited in the Indian context,<sup>10</sup> neurological manifestations were reported in 7% to 10% of the infected adults<sup>11,12</sup> and 28% of the infected children.<sup>13</sup> The prevalence of dengue encephalopathy has been estimated to range from 0.5% to 6% in patients with dengue hemorrhagic fever.<sup>14</sup> Postulated mechanisms include vasculitis with fluid extravasations, brain parenchymal edema, metabolic derangements, vascular hypoperfusion, autoimmune cross-reactivity, and,

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importantly, direct neurotoxic effects of the dengue virus.<sup>5,9,15</sup> Dengue infection leads to a wide range of manifestations from headache, fatigue, motor weakness, Guillain-Barre syndrome, seizures, meningitis, and encephalopathy to coma.<sup>7,8</sup> Patients with dengue infection and its associated complications are reported to present with psychiatric disorders such as mood disorders, anxiety disorders, personality changes, and rapid cognitive decline. This narrative review focuses on the various psychiatric manifestations of dengue infection and its sequelae, possible mechanisms, and the management options to address the psychiatric symptoms. A note is also added on the effects of histone deacetylase (HDAC) enzyme with respect to the psychiatric sequelae and the novel HDAC inhibitors that are conceptualized to be neuroprotective.

## Search Strategy

The authors (DD and VS) searched PubMed and EBSCO independently

with the following search terms: “Dengue,” “Psychiatry,” “Psychosis,” “Mania,” “Catatonia,” “Schizophrenia,” “Depression,” “Bipolar,” “Anxiety,” “Obsessive-compulsive disorder,” “psychology,” “Neuropsychiatry,” “Dementia,” and “Histone deacetylase.” We identified 226 manuscripts. The search was restricted neither to languages nor time. Manuscripts (case reports, case series, and observational studies) describing the psychiatric manifestations, in all the age groups, during the acute and convalescent phases of dengue viral infection, and their management were included for the review. The outcome of the search strategy is depicted in **Figure 1**. The total number of unique manuscripts identified for the final review was 27. This included 18 case reports, one case series, and eight observational studies. A detailed review of the eight observational studies<sup>16–23</sup> (five cross-sectional, two case-control, and one cohort study) is provided below and summarized in **Table 1**.

## Psychiatric Manifestations

Most reported patients are from Asian countries or involved travelers returning from dengue-endemic regions. Depressive disorders were the most common psychiatric presentations. During the acute phase, most (60% to 90%) patients had both anxiety and depression symptoms,<sup>16,17</sup> and syndromal depression was prevalent in 5% to 15% of patients in convalescence.<sup>20</sup> High rates (80% to 90%) of anxiety symptoms (thanatophobia) noted during the acute phase subsided during convalescence, and only 5% had persistent symptoms at three months' follow-up.<sup>16,18</sup> In another study, 62% and 59% met the criteria for depression and anxiety during the acute phase. Women had more severe depressive symptoms than men.<sup>17</sup> Severity of depression, anxiety, and stress correlated negatively with the self-efficacy scores during acute infection.<sup>19</sup> A case-control study involving pediatric population observed the prevalence of depression (13.3%) and anxiety symptoms (34.2%) during acute dengue infection to be significantly higher than matched controls.<sup>23</sup> Further, around 25% of the admitted children exhibited agitation, aggression, irritability, and visual hallucinations. Delayed psychiatric manifestations of dengue infection were reported to be predominantly depression and anxiety. At 6–24 months' follow-up after dengue infection, the rates of depression were 15%.<sup>20</sup> There are multiple case reports of manic presentation,<sup>24–31</sup> acute polymorphic psychosis,<sup>32–39</sup> prolonged depression,<sup>40</sup> and catatonia<sup>29,41</sup> and one on rapid cognitive decline.<sup>42</sup> However, the evidence for a psychotic, manic, or catatonic presentation from observational studies is lacking. It is also interesting to note that psychiatric presentations such as compulsive hoarding lead to the accumulation of trash, thereby endangering the proliferation of the *Aedes* mosquito and the increased spread of dengue. Such a possible relationship is observed in a cross-sectional study from Brazil.<sup>22</sup> Only a few studies used standard diagnostic criteria and structured psychopathology and cognition rating scales to quantify the presentation.<sup>17,18,25,26,29</sup> Most studies had little/no information on follow-up details, and retrospective studies had suggested predominant anxiety and

FIGURE 1.

### Outcome of the Literature Review

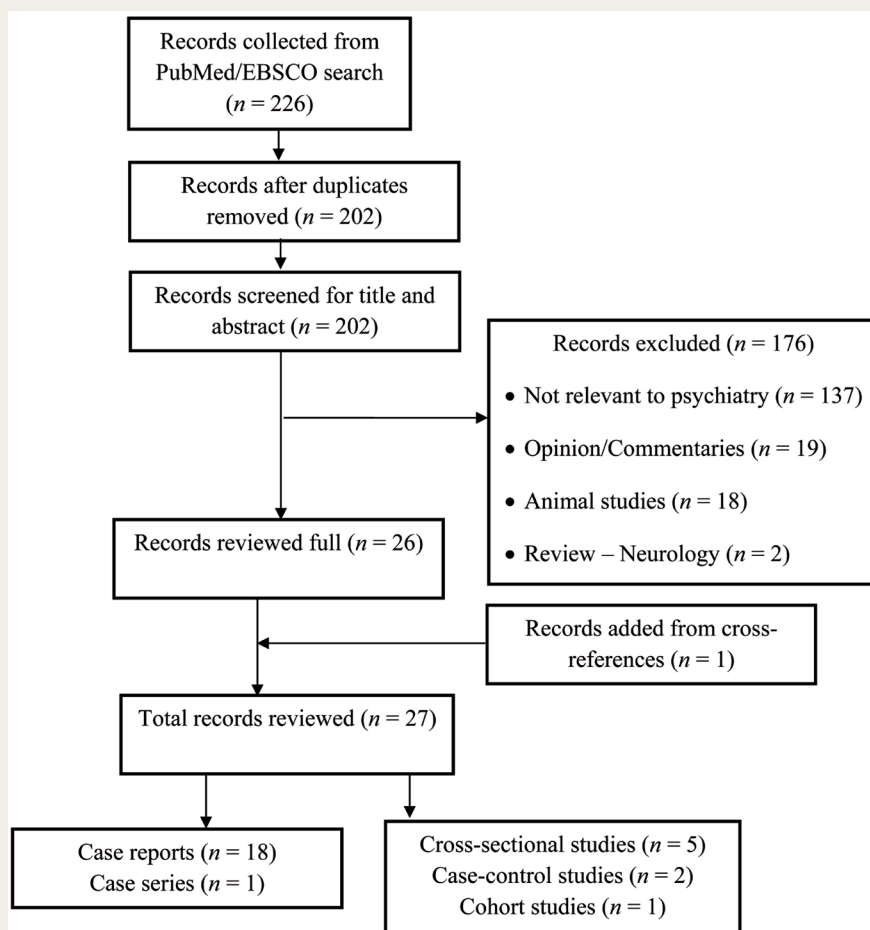


TABLE 1.

**Psychiatric Manifestations in Dengue Infection**

Study/Country/Type	Manifestations	Mechanisms	Management	Remarks
Gill et al. <sup>16</sup> (Pakistan) Prospective study n = 119	During the acute phase, almost 80% to 90% had anxiety symptoms (thanatophobia), and around 60% had depressive symptoms. The symptoms subsided soon: at recovery, only 10% had anxiety and 5% had depressive symptoms. At three months' follow-up, 5% had persistent symptoms.	Authors suggested that the development of depression in 5% of patients as an aftermath of dengue may be secondary to the individuals' personality proneness.	Reassurance reportedly alleviated anxiety in most patients. Only 20% of the diagnosed people were given benzodiazepines for anxiety. Around 5% were treated with antidepressants (medication details not provided).	Prospective evaluation provided valuable insights into the self-limiting nature of most anxiety and depressive symptoms.
Hashmi et al. <sup>17</sup> (Pakistan) Cross-sectional study n = 531 patients	62.2% met criteria for depression, and 59% met criteria for anxiety. Women had more severe anxiety and depression.	Authors postulated the possibility of inflammatory cytokines released by the infection to have played a role in psychiatric morbidity.	Psychiatric treatment provided to such patients had not been discussed in the manuscript.	HAD scale was used. Psychiatric morbidity correlated negatively with the platelet count.
Khan et al. <sup>18</sup> (Pakistan) Cross-sectional study n = 97	Among acutely ill dengue patients, around 82% had depression, and 66% had anxiety features.	Attributable mechanisms were not discussed.	Treatment provided to the patients not described.	HAD scale was used.
Mushtaq and Zahir <sup>19</sup> (Pakistan) Cross-sectional n = 200	Depression, anxiety, and stress scores correlated negatively with self-efficacy scores.	Severity of dengue infection correlated with depression and anxiety scores.	Treatment options not discussed.	DASS-21 scale was used. Self-efficacy was measured by GSES.
Gunathilaka et al. <sup>20</sup> (Sri Lanka) Case-control study n = 53 in each arm	Delayed depression, anxiety, and stress symptoms were assessed in patients who had confirmed dengue 6–24 months ago vs. age-matched controls without dengue. Dengue group had significantly more depressive, anxiety, and stress symptoms.	Clinical and subclinical viral encephalitis was postulated as the possible mechanism. Around 13% of the dengue group have had encephalopathy during the acute illness.	Treatment provided to the participants diagnosed with depression is not discussed in the report.	DASS-21 scale was used. Depression determined by psychiatrists based on DSM-5 criteria was more in the dengue group, 15.1% vs. 7.5%; however, this was not statistically significant. The mean lowest platelet count value in the study group was 62,000 cells/ $\mu$ L, which correlated positively with depressive scores.
Uvais and Moideen <sup>21</sup> (India) Descriptive study n = 14	Out of 253 dengue-infected patients, only 5% (n = 14) received any psychotropic medications. However, only 2% (n = 4) were referred for psychiatric consultation. Around 1% (n = 2) was diagnosed with depressive reaction.	Discussed the possibilities of neurotropism, capillary leakage, and release of pro-inflammatory cytokines leading to the neuropsychiatric manifestation.	Commonly prescribed psychotropics were clonazepam and quetiapine. Sertraline and amitriptyline were given for one patient each.	A retrospective descriptive study about psychotropic use in patients admitted with dengue infection.
Herbuela et al. <sup>23</sup> (Philippines) Case-control study Cases n = 255 Controls n = 260	In the pediatric population (age 8–17), during the acute phase of dengue infection, 34.2% with dengue fever had anxiety symptoms compared to 16% of controls. Around 13.3% had borderline or clinical depression compared to 3.5% in controls. Additionally, 26% reported irritability, visual hallucinations, agitation, and aggressiveness during the onset of infection.	Age and initial few days of hospitalization associated with anxiety symptoms. The presence of myalgia and arthralgia with a family history of dengue fever predicted depressive symptoms. Anxiety and depressive symptoms were postulated to be secondary to raised inflammatory markers during acute infection.	Treatment provided to children with anxiety and depressive symptoms during acute dengue infection was not discussed in the report.	Screening of psychiatric morbidities was done using the RCADS-25 scale. Specific dengue serotypes were not assessed.
<b>Psychiatric morbidity may lead to worsening of dengue spread in endemic regions</b>				
Caixeta et al. <sup>22</sup> (Brazil) Cross-sectional	Compulsive hoarding	Hoarding of trash leads to mosquito proliferation, thereby increasing the risk of dengue spread.	Not applicable.	Interesting to note that psychiatric morbidity such as hoarding might potentially worsen the spread of dengue in an endemic population.

DASS, depression anxiety stress scale; DSM, diagnostic statistical manual; GSES, general self-efficacy scale; HAD, hospital anxiety and depression scale; RCADS-25, revised child anxiety and depression scale-25 items.

depressive symptoms as chronic consequences. However, the persistence of these symptoms and the need for prolonged treatment for secondary psychiatric manifestations are not specifically described in the available studies.<sup>16,20</sup>

## Postulated Mechanisms

Although there was an argument that psychiatric presentations such as mania were mere coincidental findings during dengue fever,<sup>43,44</sup> with a rising incidence of dengue infections and growing reports of such presentations in the existing literature, it is essential to review the probable postulated mechanisms underlying psychiatric morbidity in dengue. Available observational or longitudinal studies did not elicit the etiopathogenetic mechanisms underlying psychiatric manifestations. The mechanisms postulated are largely from case reports/series and hence are anecdotal.

Interestingly, only a few reported patients with psychiatric symptoms had additional neurological manifestations such as confusion, seizures, cognitive decline, delirium, and gait disturbances.<sup>36,39,42</sup> Cerebrospinal fluid analysis showed increased protein levels and lymphocyte cells in two reports.<sup>36,39</sup> But, the analysis was considered normal in the other two reports.<sup>27,42</sup> Brain imaging studies such as computed tomography<sup>25-27,34,35,41</sup> and magnetic resonance imaging<sup>32,33,36,38</sup> in most reports were normal. Metabolic derangements, including elevated liver enzymes,<sup>24,25</sup> electrolyte abnormalities,<sup>27</sup> vasculitis with capillary leak, and fluid extravasations, were postulated.<sup>5</sup> Platelet counts ranged from 20,000 to 2,00,000 cells/ $\mu$ L,<sup>24,35</sup> and there were inconsistent correlations between platelet count and psychiatric morbidity.<sup>17,20</sup> Only four studies reported the dengue virus serotypes. DENV-2 was identified in two reports,<sup>38,39</sup> while DENV-1<sup>40</sup> and DENV-4<sup>39</sup> were associated in one report each. Direct neuronal invasion by the dengue virus was doubted for long but has been reported to be possible.<sup>26,28,45</sup> Recently, the role of secondary immune activation and epigenetic modifications in dengue-related neuropsychiatric complications has been increasingly studied.<sup>5</sup> Encephalopathy alone was not the prerequisite to psychiatric presentations, and in fact,

most patients exhibited clear sensorium during manic/psychotic breakdown, making a case for other etiological possibilities.<sup>34</sup> Further systematic studies are necessary in identifying the underlying mechanisms better.

## Management Options

Management options for the primary dengue infection are beyond the scope of the current review, and detailed reviews on the topic are available.<sup>46-48</sup> The supportive management for dengue fever primarily involves anti-inflammatory agents and corticosteroids. But, studies on psychiatric manifestations either completely neglected to report the management details of primary dengue infection<sup>17-20,23,38</sup> or did not clearly specify the agents and the doses used.<sup>16,21</sup> The literature exploring psychiatric manifestations in relation to these agents used to treat dengue is more important given the well-known association of some of them in precipitating behavioral and mood symptoms.

Only limited information is available about the management of secondary anxiety and depression symptoms. Most observational studies that aimed at understanding acute and delayed psychiatric morbidity in dengue patients did not report the treatment provided for the identified patients.<sup>17,19,20</sup> Successful management of agoraphobic symptoms with oral sertraline (dose not available)<sup>39</sup> and prolonged depression with duloxetine (dose 40 mg/day)<sup>40</sup> was reported. Mania in dengue patients was managed with antipsychotic/benzodiazepines or a combination of mood stabilizers and antipsychotic/benzodiazepines.<sup>24,26-29</sup> For psychotic presentations, a good response was achieved with oral antipsychotic agents, mostly in low doses.<sup>32-37,39</sup> Catatonic presentation responded well to intravenous lorazepam 4 mg/day, which was tapered and stopped over four weeks.<sup>41</sup>

It was noted that clonazepam and low-dose quetiapine were started for dengue patients with psychiatric comorbidity without an appropriate specialist referral. Only less than 2% of the patients with psychiatric morbidity were usually referred for formal assessment.<sup>21</sup> There is a lack of evidence on the preference of any specific psychotropics in managing psychiatric symptoms, and the chosen

treatment seems to be in line with their conventional use in general psychiatric practice.

## Histone Deacetylase (HDAC) Enzyme and Epigenetic Modifications

Histone proteins are implicated in organizing the DNA structure. Acetylation of histone proteins favors the binding of relevant transcription factors to the DNA.<sup>49</sup> Histone deacetylase (HDAC) removes histone acetylation and condense the chromatin, leading to a slowing of gene transcription.<sup>50,51</sup> After the recruitment of HDAC by factors such as DNA methyltransferase (DNMT), the silencing of promoter genes is ensured through DNA methylation.<sup>52</sup> The inactivation of genes with increased HDAC and DNMT activity has been implicated in the manifestation of psychiatric conditions.<sup>53</sup>

HDAC enzymes are classified into two families, four groups, and 18 isoforms (HDAC 1-11 and silent information regulator-2 related proteins 1-7).<sup>49,54</sup> Virus-mediated gene transduction was shown to result in altered HDAC activity, impairing neuroplasticity and cognition.<sup>55</sup> Dengue infection, especially hemorrhagic fever, was reported to result in a "cytokine storm" characterized by elevated levels of circulating cytokines and chemokines.<sup>5</sup> Cytokine storm following dengue infection may lead to oxidative stress, which promotes the HDAC activity.<sup>56,57</sup> (Inflammatory mechanisms were postulated in the etiopathogenesis of bipolar disorder in animal models.<sup>58</sup> HDAC overexpression in adult mouse hippocampus was reported to result in decreased prepulse inhibition. This aberration was described in both human and animal models of schizophrenia.<sup>59,60</sup> Such epigenetic modifications play a crucial role in understanding the etiopathogenesis of most psychiatric disorders.)

## Role of HDAC Inhibitors in Treatment

Numerous preclinical studies reported the antimanic effects of HDAC inhibitors. Valproate is a potent inhibitor of HDAC and has been used as a mood stabilizer for decades.<sup>49,61</sup> Carbamazepine and topiramate are also reported to inhibit HDAC to some extent, while

other antiepileptics such as levetiracetam, phenobarbitone, or gabapentin did not inhibit HDAC.<sup>62-64</sup> The ability of lithium to inhibit HDAC has not been elucidated.<sup>65</sup> However, lithium plays a role in gene transcription regulation through glycogen synthase kinase-3 inhibition.<sup>66</sup>

Interestingly, chronic exposure to second-generation antipsychotic drugs has been reported to result in overexpression of HDAC2 and thereby proposed to result in cognitive dysfunction.<sup>55,67</sup> Quetiapine was shown to reduce DNMT, a close associate of HDAC, in the hippocampus and nucleus accumbens, thereby reducing DNA methylation in animal models and also promoting hippocampal neurogenesis.<sup>63,68,69</sup> The HDAC/DNMT inhibitors reactivate the suppressed genes, which ultimately results in clinical improvement<sup>53</sup> (see **Figure 2**).

Inhibition of Class I and Class III HDACs was reported to promote antidepressant action of fluoxetine, while additional inhibition of Class II HDACs was required to promote anti-anxiety action of the molecule.<sup>70</sup> In animal models, high-frequency repetitive transcranial magnetic stimulation was reported to promote histone acetylation and gene expression.<sup>71</sup> Selective HDAC2 isoform inhibitors were reported to ameliorate cognitive deficits in animal models.<sup>72</sup>

In our review, generally, the prognosis of psychiatric morbidity following dengue was good. Seven of the reviewed reports utilized any one agent (valproate, quetiapine, or carbamazepine) with

HDAC/DNMT inhibition.<sup>24-29,31,34</sup> These reports suggested an early and favorable outcome. However, reports utilizing other agents without HDAC/DNMT inhibition also suggested favorable outcomes. Clinicians are recommended to follow appropriate precautions while prescribing HDAC inhibitors such as valproate and carbamazepine to women in the childbearing age group because of high teratogenicity and other side effects. The role of HDAC inhibitors in treatment is limited, owing to the lack of specificity for selective HDAC isoforms and severe side effects such as teratogenicity, cytotoxicity, polycystic ovarian syndrome, etc.<sup>73,74</sup>

## Conclusion and Future Directions

The dengue epidemic is on the rise for two decades. Neurological and especially psychiatric manifestations are increasingly reported in acute as well as convalescent phases of dengue infection. Frank psychiatric manifestations without neurological consequences are also reported, with mood disorders being the commonest. A cytokine storm unleashed by dengue infection potentially leads to significant neuropsychiatric manifestations. Proposed etiopathogenesis involves epigenetic mechanisms such as overexpression of HDAC enzymes. Mood stabilizers such as valproate and second-generation antipsychotics such as quetiapine and clozapine show inhibition of DNA methylation. These agents provide clinical scope and utility to manage post-dengue psychiatric

manifestations. However, the specificity of HDAC class and isoforms associated with psychiatric symptoms needs further delineation. The development of HDAC isoform-specific inhibitors might improve the clinical application, with reduced side effects. The authors consider that the following steps are essential in improving the understanding of psychiatric manifestations and management of dengue infection.

1. Documentation of phenomenological psychiatric presentations.
2. Delineating neurological consequences (seizures, encephalitis, confusion, etc.).
3. Reporting the identified dengue serotype involved and other relevant immunological investigations.
4. Reporting the details of treatment provided and the response.
5. Following up for longitudinal consequences.
6. Systematic studies to evaluate the association and effectiveness of psychotropic agents that have properties of modulating specific epigenetic factors in dengue-related psychiatric disorders.

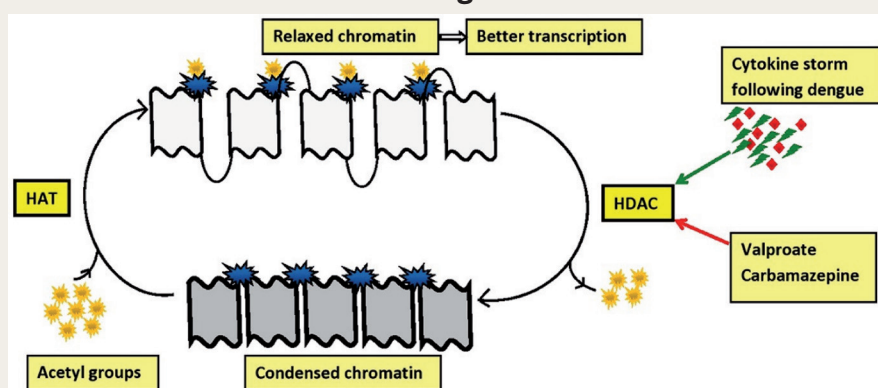
Despite reporting a significant proportion of dengue infections, longitudinal studies describing the neuropsychiatric manifestations and its management are a few from India. Multidisciplinary research is the need of the hour. Clinical suspicion regarding comorbid depression and anxiety, with an appropriate referral for psychiatric consultation, would ultimately result in better outcomes. Longitudinal studies are sparse and, whenever available, are with further limitations such as neuropsychiatric manifestations being assessed without standardized tools, inadequate attention paid to postulating possible mechanisms, and describing the treatment options used. The development and availability of vaccines to prevent dengue infection are in their early stages. Systematically designed prospective studies with the suggested steps might elucidate the pathogenesis of dengue-related psychiatric consequences and probably shed light on novel treatment options.

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FIGURE 2.

### Role of HDAC Inhibitors in Relaxing the Chromatin



HDAC, histone deacetylase enzyme; HAT, histone acetyltransferase enzyme.

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