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NEUROBIOLOGICAL ASPECTS OF SUICIDE AND SUICIDE ATTEMPTS IN BIPOLAR DISORDER

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Abstract

Suicide and bipolar disorder (BD) are challenging, complex, and intertwined areas of study in contemporary psychiatry. Indeed, BD is associated with the highest lifetime risk for suicide attempt and completion of all the psychiatric conditions. Given that several clinical risk factors for both suicide and BD have been well noted in the literature, exploring the neurobiological aspects of suicide in BD may provide insights into both preventive measures and future novel treatments. This review synthesizes findings regarding the neurobiological aspects of suicide and, when applicable, their link to BD. Neurochemical findings, genes/epigenetics, and potential molecular targets for current or future treatments are discussed. The role of endophenotypes and related proximal and distal risk factors underlying suicidal behavior are also explored. Lastly, we discuss the manner in which preclinical work on aggression and impulsivity may provide additional insights for the future development of novel treatments.

Keywords

Suicide; Suicidal behavior; Bipolar disorder; Glutamate; Neurobiology; Depression; Treatment

Introduction

Of all the psychiatric conditions, bipolar disorder (BD) is associated with the highest lifetime risk for suicide attempt and completion [1]. Indeed, the lifetime risk of completing suicide in patients with BD ranges from 8–20%, nearly 10–20 times that of the U.S. general population [2]. Strikingly, between 25% and 56% of patients with BD attempt suicide; many of those who survive experience resulting morbidity and, on average, have shorter life expectancies [3,4]. The World Health Organization's Global Burden of Disease study ranked BD seventh among all medical disorders with regard to years of life lost to death or disability [5]. Although several clinical risk factors for suicide have been noted in the literature [6,7], most research in this area has focused on the stress-diathesis model of suicidal behavior [8–11] and on evaluating potential proximal and distal risk factors [12] (see Tables 1 and 2). Nevertheless, suicidal behavior remains extremely difficult to predict even when comprehensive clinical and neurocognitive information is available [13]. Thus,

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understanding the neurobiological aspects that underlie suicidal behavior may provide important insights into more effective preventive measures and/or future novel treatments.

The concept of suicide as a neurobiological phenomenon emerged in the mid-1960s in response to a seminal study that noted increased mean urinary levels of 17-hydoxycorticosteroid (a metabolic product of cortisol) in depressed patients who went on to commit suicide [14]. Since then, many studies have explored the neurobiological underpinnings of suicide using a variety of approaches, including post-mortem brain tissue analysis, changes in cerebrospinal fluid (CSF), and alterations in peripheral markers in suicide completers compared to matched control groups. Each of these methods is associated with significant limitations and confounders. In postmortem studies, such confounders include prior medication exposure status, proxy-based psychiatric diagnoses, integrity of the samples, variability in postmortem interval, and co-morbid substance abuse. Similarly, the limitations of using *in vivo* samples include the temporal relationship between the time of the suicide attempt and the point of collection, and the inability to establish the presence or lack of suicidal ideation in attempters. Despite limitations, post-mortem methods are still valuable for in-depth molecular and cellular analyses not otherwise possible in living subjects [15].

Table 3 highlights findings from several excellent reviews that detail neurobiological alterations associated with suicide/suicidal behavior [8,9,12,16–20]. It is beyond the scope of this review to explore all of these topics; instead, this article selectively discusses those findings and clinical trials that clinicians may find of greatest value. It should be noted that, across the literature, many of these findings are inconsistent, and not all are specific to BD. However, it has been argued that the vast majority of suicide attempters and victims suffered from an underlying mood disorder at the time of the attempt [21,22]. As a result, these findings may very well be relevant or have overlapping involvement in BD, and positive findings may ultimately lead to new targets and enhance subsequent drug discovery efforts [23].

Neurochemical findings in target systems

Decades of research have documented abnormalities in the hypothalamic pituitary adrenal (HPA) axis as well as the serotonergic, dopaminergic, and noradrenergic systems with regard to the neurobiology of suicide. These systems are integral to stress response, and their altered functioning may be influenced by genetic, epigenetic, and/or adverse life events [18].

Serotonergic system

As regards the serotonergic system, depressed patients with suicidal behavior were found to have significantly lower CSF levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) than depressed patients without suicidal behavior or controls [24–26]. Low CSF 5-HIAA levels were also shown to predict future suicide attempts and completions [27,28]. Interestingly, lower levels of the same metabolite were shown to correspond with the lethality of the suicide attempt [29]. Similarly, low serotonergic function was observed in suicide attempters with major depressive disorder (MDD), as indicated by a blunted prolactin response to challenge dosing with a serotonin reuptake inhibitor, fenfluramine [30]. Among the many serotonin (5-HT) receptor subtypes, extensive postmortem studies implicate 5-HT_{2A} receptors [19]. Early studies found increased 5-HT_{2A} binding in suicide victims compared to controls [31], and subsequent studies similarly showed patterns of increased protein expression of 5-HT_{2A} in the prefrontal cortex (PFC) and hippocampus in suicide victims [32]. It thus appears that post-synaptic serotonin receptor upregulation reflected in increased gene expression may be a compensatory response to reduced serotonin neuronal activity [32].

Noradrenergic system

Fewer noradrenergic neurons were found in the loci cerulei of suicide victims with MDD [33], and increased β-adrenergic receptor binding was found in the PFC of suicide victims [34]. In addition, lower urinary and plasma levels of 3-methoxy-4-hydroxyphenylglycol (MHGP), a major metabolite of norepinephrine, were found in patients displaying suicidal behaviors compared with controls [35]. Another study found that the lethality of suicide attempts in BD patients negatively correlated with MHGP levels [36].

Dopaminergic system

Few post-mortem studies examining the dopaminergic system have shown conclusive trends; however, one study demonstrated higher cortical levels of homovanillic acid (HVA) (dopamine's primary metabolite) in suicide and homicide victims compared to those who died of physical disease, but not accident victims [37]. High CSF levels of HVA have also been shown to correlate with human aggression [38].

HPA system

With respect to the HPA axis, considerable evidence suggests that early-life adverse events can produce enduring changes in the regulation of stress-response systems in humans [39,40]. In addition, the HPA axis has bidirectional relationships with the neurotransmitter systems discussed above [41]. As a result, many investigators have examined components of the HPA axis in suicide victims. For example, one postmortem study identified a significant decrease in the number of corticotropin releasing factor (CRF) receptor binding sites in suicide completers compared to controls [42]. Similarly, increased CRF immunoreactivity was found in the frontal cortex of suicide victims [43]. A recent study also demonstrated that BD patients with a past history of attempted suicide had bedtime salivary cortisol levels 7.4% higher than unaffected healthy controls [44]. BD alone was not associated with a cortisol increase, suggesting a role for stress dysregulation in mediating the high suicide risk in BD.

Interestingly, the dexamethasone suppression test (DST), a measure used to assess HPA axis functioning, showed that non-suppressors were more likely to commit and complete suicide than DST suppressors over long-term follow-up (e.g. 15 years) [45–47]. A recent meta-analysis of seven studies concluded that DST non-suppression increased suicide risk by a factor of 4.6 [48]. The DST has also been explored as a potential biological marker for depression [49,50] and, indeed, DST non-suppression has been associated with severity and poorer prognosis in major depressive episodes, suggesting that it may be a potential state-dependent marker for suicide risk [8]. DST non-suppression has also been found more often in the depressed phase of BD compared to patients with MDD [51]. For additional neurobiological findings regarding HPA dysfunction and suicidal behavior, the interested reader is referred to an excellent review by Turecki and colleagues [12].

Other hormonal systems: cholesterol and testosterone

The link between lipids and suicidal behavior was investigated after large randomized clinical trials and other meta-analyses revealed an increase in violence-related activities—including suicide [52,53]—in patients taking cholesterol-lowering medications. Specifically, clinical studies suggested a relationship between reduced total cholesterol levels and suicidal behavior [54–56]. One recent study found lower serum cholesterol and triglyceride levels in men with BD who attempted suicide compared with BD men who had not [57]. Additional support for this potential biological marker comes from a study noting that the biological relatives of Smith-Lemli-Opitz syndrome carriers—an autosomal recessive condition characterized by abnormally low cholesterol levels resulting from mutations in the genes

involved in cholesterol biosynthesis—had an increased number of suicide attempts and completions compared to controls [58]. Low cholesterol levels have been associated with decreased serotonergic activity [59] and lower cholesterol in the brain, which may lead to reduced synaptic plasticity and brain dysfunction [60]. As a result, Smith-Lemli-Opitz patients and carriers may be important sub-groups for further study with regard to suicide neurobiology.

A recent exploratory study in male and female BD patients experiencing a depressive or mixed episode who had at least one past suicide attempt found that testosterone levels were positively correlated with both the number of previous manic episodes and with suicide attempts [61]. Notably, cholesterol serves as a precursor to testosterone and other hormones such as cortisol and estrogen. While the relationship between serum testosterone levels and suicidal behavior is not consistent [62], testosterone and other androgens are believed to be involved in the pathophysiology of mood disorders and suicidal behavior [63,64].

Genetics and epigenetics

Between twins, heritability estimates for suicide range from 21–50%, and 30–55% for suicidal behavior (attempts, suicidal ideation, planning) [65]. Both linkage and association studies can be used to identify relevant genes and pathways associated with suicide. While it is beyond the scope of this review to offer a comprehensive overview of this large and rapidly growing field, it should be noted that several new technologies are powering this research, including emerging microarray technologies and functional genomic studies that can profile the expression of thousands of genes and perform genome-wide arrays for thousands of single nucleotide polymorphisms (SNPs) [66].

Genetics

An earlier systemic review of association studies evaluating suicidal behavior and genes coding for serotonin receptors and for the serotonin transporter gene *(5-HTT)* noted a significant, robust association with the *5-HTT* promoter locus, but not for the *5-HT2A* 102 T/C variant. The review, which included a meta-analysis of nearly 12 studies (n=1599), found a significant association between the *5-HTTLPR* low-expressing S allele and suicidal behavior [67]. Other candidate genes have included tryptophan hydroxylase *(TPH 1* and *TPH 2)*, catechol-O-methyltransferase *(COMT)*, and nitric oxide synthase types I and III (*NOS I* and *NOS III*) [68–70]. A recent analysis of genome-wide association studies of BD-I and BD-II, as well as MDD, found that the strongest association for suicide attempts in BD was observed in a region without identified genes (rs1466846). While five other loci showed suggestive associations, overall results suggested that the inherited risk for suicide in mood disorders is unlikely to be secondary to individual common variants of large effect [71].

Candidate genes for association studies in suicide have generally been drawn from prior neurobiologic studies that identified many of the systems described above as putative targets; in addition, areas related to neurotrophins and cell signaling systems are now also being investigated [72]. A recent review by Pandey and colleagues discussed the role of key transcription factors and target genes involved in suicide [19]. Most studies discussed used postmortem brain samples, and results broadly implicate serotonin subtype receptor abnormalities, along with variations in G proteins, the effector phospholipase C (PLC), and protein kinases A and C (PKA and PKC) (see Table 3) [19]. PKC activates the transcription factor cyclic adenosine monophosphate response element-binding protein (CREB) that, in turn, regulates the expression of target plasticity genes such as brain derived neurotrophic factor (BDNF). Interestingly, studies have shown decreased CREB and BDNF (along with tyrosine related kinase (TrkB) receptors) in the postmortem brains of suicide victims [73–75].

Epigenetics

The study of epigenetics, a relatively new branch of molecular biology, may provide insight into the way the environment influences gene expression by examining phenotypic changes not coded by DNA. Common epigenetic mechanisms include DNA methylation, histone acetylation/deacetylation, and phosphorylation. One recent study reported epigenetic alterations in suicide victims; DNA methyltransferase (DNMT) 3b (an enzyme that *de novo* methylates CpG islands) had increased expression in the frontopolar cortex of suicide completers compared to controls [76]. Similarly, another study implicated altered TrkB expression in epigenetic processes related to suicide [75]. However, caution must be employed in assuming that epigenetic changes are involved in particular disease/outcome states, as this field is still evolving; more knowledge is required to understand how these alterations are mediated [77].

Endophenotypes and potential medication targets

Suicide endophenotypes: impulsivity and aggression

The concept of candidate suicide endophenotypes is also being used to explore the neurobiological basis of suicide [78–81]. Prominent researchers have defined an endophenotype as a “measurable component along the pathway between disease and distal genotype” [82]. Endophenotypes include neurophysiological, biochemical, and neuropsychological constructs, where heritability and stability (state independence) represent key components of an ideal marker [78]. In particular, impulsivity and aggression have been well studied candidate endophenotypes associated with suicidal behavior [79]. Other endophenotypic approaches include studying impaired decision-making, altered skin conductance, and response to functional neuroimaging paradigms [80]. Overall, these constructs could be used in conjunction with other endophenotypes already explored in BD, including abnormal regulation of circadian rhythms, response to certain medication challenges, cognitive deficits, and neuroimaging findings (e.g. early-onset white matter abnormalities) [83,84] to better predict suicidal behavior.

With respect to BD patients, a recent regression analysis showed that lifetime aggressive traits were associated with past suicide attempts [85]. Interestingly, previous studies have suggested that lithium may have strong anti-aggressive properties in humans [86,87] and anti-impulsivity properties in preclinical models [88–90]. Notably, of all current treatments for BD, long-term lithium therapy is the only intervention associated with decreased rates of suicidal behavior and mortality in well-conducted meta-analytic reviews [91–93]. Putative molecular targets for lithium include cyclic adenosine monophosphate (cAMP)-mediated signal transduction, CREB activation, increased BDNF expression, the phosphatidylinositol cascade, PKC inhibition, glycogen synthase kinase 3 (GSK-3) inhibition, and B-cell lymphoma 2 (Bcl-2) expression [94]. Complementary work has also been undertaken to develop relevant animal models of suicide (e.g. shock-induced aggression) in order to test potentially protective pharmaceutical compounds [78,95].

Nevertheless, a recent, randomized, double-blind trial evaluating lithium compared to valproate detected no difference between treatments with regard to time to suicide attempt or suicide event [96]. However, it should be noted that given the challenge of recruiting very ill BD patients for research, the authors were not able to meet their target enrollment; as a result, the study was significantly underpowered to detect suicide deaths or suicide attempts. Similarly, the study may not have been enriched for impulsive suicidal individuals. These findings should not discourage practitioners from using lithium as a first-line agent in BD; indeed, a recent editorial highlights the ethical, logistic, and feasibility hurdles involved in conducting such “hard outcome” clinical studies [97]. Table 4 summarizes other valuable randomized controlled studies that evaluated suicide or suicidal behavior as the primary

outcome in their clinical trials. In addition to lithium, clozapine—although primarily used to treat schizophrenia—has also been shown to reduce suicidal behavior [98,99]. With regard to clozapine's putative mechanism of action, one animal study found that clozapine inhibits system A-mediated glycine transport in cortical synaptosomes [100]. System A transporters may play a role in regulating synaptic glycine levels and provide an indirect mechanism for clozapine to potentiate N-methyl-D-aspartate (NMDA) receptor mediated neurotransmission [100].

Finally, studying other syndromes with features that contribute to suicide risk (e.g. increased impulsivity) may generate other neurobiologic targets. For example, children affected with Lesch-Nyhan syndrome, a rare inherited condition characterized by overproduction and accumulation of uric acid, will often have an irresistible urge to hurt themselves (e.g. biting, head banging). Interestingly, allopurinol, a xanthine oxidase inhibitor used to treat hyperuricemia has been shown to be effective in treating mania [101–103]. Impulsivity in mania is pervasive, known to affect attention and behavioral inhibition, and can often lead to suicide attempts [104]. Interestingly, an experimental D1 dopamine receptor antagonist is currently being evaluated to relieve self-injurious behavior in patients with Lesch-Nyhan syndrome (NCT01065558). Table 5 highlights potential medication targets for decreasing suicidal behavior.

Novel drug developments

Ketamine

Remarkably, a recent experimental therapeutic has also demonstrated promising anti-suicidal effects. An open-label study found that a low, intravenous dose of the NMDA antagonist ketamine (0.5 mg/kg)—previously shown to have rapid antidepressant effects in randomized controlled trials of MDD [105] and bipolar depression [106]—rapidly (within 40 minutes) and significantly decreased suicidal ideation scores. This effect remained significant for four hours post-infusion [107]. Another study found that ketamine was associated with reductions in the suicidality item score in the Montgomery-Asberg Depression Rating Scale (MADRS) scale and with other implicit suicidal associations within 24 hours after a single infusion [108]. Another recent trial that replicated ketamine's antidepressant effect in bipolar depression also found that this agent rapidly improved suicidal ideation [109]. In addition, a recent naturalistic study with low-dose ketamine (IV bolus 0.2mg/kg over one to two minues) in depressed emergency room patients with acute suicidal ideation found significant improvements in suicidal ideation that lasted up to 10 days post-infusion [110]. A large, randomized, double-blind trial evaluating ketamine for suicidal ideation is currently underway (NCT01507181).

Mechanisms underlying ketamine's rapid antidepressant effects have implicated costimulation (along with NMDA receptors) of α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) ionotropic receptors and several downstream signaling cascades including the serine/threonine protein kinase mammalian target of rapamycin (mTOR) pathway and GSK-3. Ketamine's mediated blockade of NMDA receptors has also been shown to deactivate eukaryotic elongation factor (eEF2), leading to reduced eEF2 phosphorylation and de-suppression of rapid dendritic protein translation (including BDNF) [111]. Ketamine similarly activates cytoskeleton-associated protein (Arc), which is involved in actin polymerization and stable expansion of dendritic spines. These dynamic processes overall contribute to the synaptic plasticity mechanisms that mediate ketamine's rapid antidepressant effects [112]. As such, these targets—including GSK-3 inhibition— may also be responsible for ketamine's rapid antisuicidal effects. Future studies will aim to further elucidate this area of investigation.

Thyrotropin-releasing hormone

The antisuicidal effects of intranasal thyrotropin-releasing hormone (TRH) are now being evaluated. TRH is a hypothalamic tripeptide-releasing hormone that stimulates the pituitary release of thyroid stimulating hormone (TSH), thus regulating the production of thyroid hormones. TRH receptors are found throughout the brain, with highest densities occurring in the amygdala and hippocampus and lower levels in the cortex, diencephalon, and basal ganglia [113]. Since the 1970s, TRH has been relevant to the pathophysiology of mood disorders; early studies evaluating the rapid antidepressant effects of oral and intravenous TRH had mixed results (reviewed in [114]). Challenges with this agent include minimal blood-brain barrier penetration and rapid degradation of TRH in the periphery given its short half-life [115]. Nevertheless, one pilot study (n=8) that used a lumbar intrathecal (IT) injection (half-life 54.5 +/− 5.4min in CSF) of TRH (500μg of protirelin) found that it had both rapid antidepressant and antisuicidal effects [115]. The authors cautioned against generalizing the results due to the small sample size and refractory patient population. In addition, no subsequent studies replicated this finding. Nevertheless, TRH may lead to promising avenues in suicide research, particularly with respect to therapeutic options that could emerge from efforts to optimize delivery routes.

Conclusions

Suicide is a significant, longstanding public health issue. Individuals with BD are at significantly higher risk of morbidity and mortality from suicidal behavior than the general population. As noted above, a great deal of research has focused on dysfunction of the HPA axis and alterations of major neurotransmitter systems. Glutamatergic involvement may play an important role, given recent antisuicidal findings with the NMDA antagonist ketamine [116]. Additional research has also emerged at the gene/epigenetic level, and from the study of neurotrophic factors and lipid metabolites. Future studies will investigate proximal and distal risk factors with various endophenotypes underlying suicidal behavior. Unfortunately, designing meaningful clinical trials to study proximal risk factors such as suicidal ideation, while necessary, is fraught with ethical and logistical challenges. With respect to new compounds, preclinical work in the areas of aggression and impulsivity may provide additional insights for drug development. Novel therapeutics such as ketamine and the repurposing of TRH may also meaningfully contribute to future preventive measures.

Kim and colleagues suggested a model to predict suicide risk that uses a classification system similar to the Child-Pugh classification system used in chronic liver disease [117]. In this model, points would be assigned to risk factors such as DST-non suppression, lower CSF-5-HIAA levels, abnormal neuropsychological test results, genetic factors, cholesterol levels, and validated psychosocial risk factors. As the cost of neuroimaging decreases, these technologies could further be applied in clinical populations. While such models have limitations (e.g. low specificity [50]), hypothetically the total scores of these accumulated risk factors would correlate with suicide risk.

Finally, future treatments should not solely focus on suicide molecular “targets”, but continue to address comorbid conditions associated with suicide. Results from the National Comorbidity Survey Replication study revealed that approximately 80% of those who attempt suicide in the United States have a prior mental disorder; in particular, the comorbid presence of disorders characterized by severe anxiety/agitation (e.g. PTSD) and poor impulse control (e.g. substance abuse disorders) may predict which individuals with suicidal ideation go on to plan or attempt suicide. Future studies will need to examine the bi-directional interaction between such comorbidities and molecular targets of suicide to point to therapeutic anti-suicide targets and to better estimate overall suicide risk in individuals [118]. To further address risk, combining non-pharmacological approaches (e.g. cognitive

behavioral therapy, dialectical behavior therapy) with evidence based medication regimens may also reduce suicide risk in BD [119]. Because suicide is a complex phenomenon and requires a multidimensional approach, the time to conduct rigorous studies applying neurobiological frameworks to reduce suicide and suicidal behavior is now.

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Table 1

Clinical variables significantly associated with suicidal behavior in patients with bipolar disorder.

Risk factors	Adjusted odds ratio
Female gender	2.08
History of alcohol abuse	2.05
History of substance abuse	1.99
Current benzodiazepine use	1.59
Higher overall symptom severity	1.45
Treatment non-adherence	1.40
Greater depressive symptom severity baseline	1.09
Longer disease duration	1.02
Young age at first treatment for mood episode	0.98

Adapted from: Bellivier *et al.,* 2011 [7]

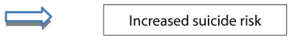
Study design: Two-year, prospective, observational study that enrolled 3,684 adult patients with bipolar disorder and initiated or changed oral treatment for an acute manic/mixed episode

Table 2

Suicide models.

Adapted from: Mann *et al.*, 2003 [8]

Distal risk factors	Proximal risk factors
Family history of suicide & genetic factors	Recent life events
Early life adversity	Psychopathology
Personality traits and cognitive styles	Suicidal ideation
Chronic substance abuse	Hopelessness



Adapted from: Turecki *et al.*, 2012 [12]

Table 3

Summary of putative targets explored in the neurobiology of suicide.

Neurotransmitters	Examples of findings in suicide victims/Attempters compared to controls	Citation
Serotonin	Decreased 5-HIAA levels in CSF; decreased serotonin uptake and transporter levels in platelets; blunting of fenfluramine-induced prolactin response; increased 5-HT_{1A} and 5-HT_{2A} receptor binding and expression in PFC; increased TPH immunoreactive neurons in DRN, 5-HTT promoter	[24,25,28,31,32,67,120–129]
Norepinephrine/Adrenaline	Lower urinary and plasma MHPG (major metabolite of NE); MHPG levels negatively correlated with lethality of attempts; fewer noradrenergic neurons in LC; increase in α2-adrenergic receptor densities and mRNA expression in hypothalamus and frontal cortex; increased β-adrenergic binding	[33,35,130,131] [34,132–135]
Dopamine	Lower CSF HVA; lower urinary HVA, DOPAC, and dopamine	[136,137]
Glutamate and glial involvement	Density of AMPA receptors may be increased in caudate nucleus; downregulation of SLC1A3 and GLUL and other differential gene expression; elevated microglial density; alteration in NMDA receptor complex in frontal cortex	[138,139–143]
GABA	Increased density of GABA neurons in hippocampus/neocortical areas; upregulation of $GABA_A$α5 in frontal cortex; increase in relative density of GAD-ir neuropil in hippocampal formation; differential gene expression	[139,141,142,144,145]
Opioids	Higher density of μ-opioid receptors in frontal and temporal cortex	[146]
Acetylcholine	Increased [^{3}H]-pirenzepine binding of M1 and M4 receptor binding in ACC	[147]
Cell signaling		
G-proteins	Lower basal and GTPγS-simulated AC activity; decreased GTPγS-stimulated PI hydrolysis and decreased G_Sα protein expression in BA 10; decreased levels of G_{i2}α and G_Oα and increased levels of G_Sα-S in PFC	[148–150]
Phospholipase C (PLC)	Decreased protein expression of isoenzymes in PFC	[151]
Protein Kinase C (PKC)	Decreased PKC activity in PFC	[152–154]
Protein Kinase A (PKA)	Decreased protein and mRNA expression of PKA subunits of PFC	[155,156]
CREB	Decreased protein and mRNA expression in PFC and hippocampus	[73,74]
BDNF and Trk-B receptor	Decreased mRNA expression of BDNF and Trk-B isoforms noted in postmortem brain	[75,157]
Stress systems		
HPA Axis	Decreased CRF receptors and altered CRF receptor type ratios; higher POMC mRNA density; increased levels of CRF immunoreactivity; DST-non-suppressors more likely to commit and complete suicide; increased adrenal weight; altered GR mRNA expression	[42,43,46,158–165]
Polyamines	SSAT downregulation in frontal cortex; upregulation of ARG2, AMD1, OAZ1, and OAZ2 (roles in polyamine biosynthesis)	[166,167]
Cytokines	Increased mRNA expression of IL-4 in PFC of females and increased IL-13 in males; increased IL-6 levels in CSF; elevated quinolinic acid in CSF of suicide attempters	[116,168,169]
Testosterone	Testosterone levels positively correlate with number of manic episodes and number of suicide attempts	[61]
Others		
Lipid metabolism	Lower levels of serum cholesterol and triglycerides; increased suicidal behaviors in Smith-Lemli-Opitz syndrome; lower serum concentrations of the n-6, arachidonic acid (AA) in subjects with suicide attempts	[55,57,58,170,171]

Neurotransmitters	Examples of findings in suicide victims/Attempters compared to controls	Citation
Epigenetics	Increased cytosine methylation of NR3C1 glucocorticoid receptor promoter; increased DNMT 3b mRNA expression; increased histone methylation; increased BDNF promoter methylation in Wernicke area	[76,164,172,173]
Cognitive alterations	Impaired decision making (Iowa Gambling Task); increased attentional bias toward suicide-related stimuli; impairments in neuropsychological tasks (e.g. attention/memory)	[174–178]

Abbreviations:
CSF – cerebrospinal fluid; 5-HIAA - 5-Hydroxyindoleacetic acid; TPH – tryptophan hydroxylase; DRN – dorsal raphe nucleus; 5-HTT – serotonin transporter; NE – norepinephrine; MHPG - 3-Methoxy- 4-hydroxyphenylglycol; LC – locus coeruleus; mRNA – messenger ribonucleic acid; HVA – homovanillic acid; DOPAC – dihydroxyphenylacetic acid; AMPA - α-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid; GABA - gamma-aminobutyric acid; GAD – glutamic acid decarboxylase; ir – immunoreactive; M1 and M4 – muscarinic acetylcholine receptors; ACC – anterior cingulate cortex; CREB - cAMP response element-binding protein; GTP – guanosine triphosphate; AC – adenylyl cyclase; PI – Phosphatidylinositol; BA – Brodmann area; PFC – prefrontal cortex; BDNF - brain-derived neurotrophic factor; Trk-b – tyrosine related kinase; HPA – hypothalamic-pituitary-adrenal; DST - dexamethasone suppression test; CRF - corticotropin-releasing factor; GR- glucocorticoid receptor; POMC - pro-opiomelanocortin; ARG2 - arginase II; AMD1 - S-adenosylmethionine decarboxylase; OAZ1 and OAZ2 - antizymes 1 and 2; SSAT - Spermidine/spermine N1-acetyltransferase; IL – interleukin; SLC1A3 - solute carrier family 1 (glial high affinity glutamate transporter) member; GLUL – glutamate-ammonia ligase; NR3C1 - neuron-specific glucocorticoid receptor; DNMT - DNA methyltransferase

Table 4

Summary of randomized medication trials evaluating suicidal ideation/Behavior as a primary outcome.

Study	Design/Sample	Primary measures	Results	Citations
Grunebaum *et al.* (2012)	DB, RCT n=74, paroxetine (max 50 mg/d) vs. bupropion (max 450 mg/d), MDD pts with hx of suicide attempt or SI, 16 wks	Suicidal attempt classification by weekly consensus; suicidal events by Columbia Suicide History Form; SSI	Depressed patients with greater baseline SI treated with paroxetine compared to bupropion appeared to experience greater acute improvement in suicidal ideation, after adjusting for global depression	[179]
Oquendo *et al.* (2011)	DB, RCT, n=98, BD with past suicide attempts, lithium vs. valproate, 2.5 yrs	Time to suicide completion; time to suicide attempt; time to suicide event; SSI	Intent-to-treat showed no differences between treatment groups in time to suicide attempt or to suicide event	[96]
Khan *et al.* (2011)	DB, RCT, parallel group; MDD; citalopram (20 mg/d) + placebo vs. citalopram + lithium (300 mg/d), n=80, 4 wks	At screening and trial end: suicidal thoughts/behaviors; S-STS; MADRS; C-SSRS	No significant differences in primary outcome measures at 4 wks; post-hoc analysis showed patients assigned to citalopram + therapeutic lithium had significantly higher S-STS remission rates.	[180]
Rucci *et al.* (2011)	Two-site, RCT, MDD, allocated to IPT or SSRI, n=291, 4 months	SI; Suicidality items from HDRS and QIDS	Time to suicidal ideation was significantly longer in patients allocated to SSRI compared to those allocated to IPT, even after controlling for treatment augmentation, benzodiazepine use, and co-morbidity with anxiety disorders	[181]
Lauterbach *et al.* (2008)	DB, RCT, pts with recent suicide attempts (<3 months), treatment with lithium or placebo, n =167, 12 months	Suicide attempt; SSI	Survival analysis showed no significant difference of suicidal acts between lithium and placebo. Post-hoc analysis revealed that all completed suicides had occurred in the placebo group, accounting for a significant difference in incidence rate	[182]
Reeves *et al.* (2008)	DB, RCT, placebo-controlled, n=24, MDD on antidepressant receiving risperidone (0.25 mg – 2 mg/d) vs. placebo, 8 wks	Severity of suicidality; SSI	Risperidone significantly reduced SI in MDD patients and the overall effect of risperidone appeared to be superior to placebo. The onset of effect was within 2 weeks of treatment and sustained along the course of the treatment.	[183]
Lauterbach *et al.* (2005)	DB, RCT, placebocontrolled multi-center trial evaluating proposed suicide preventive effects of lithium in patients with suicidal behavior	Number of suicide attempts or completed suicides; SIS; Medical Damage Scale; Risk-Rescue Scale; SSI	SUPLI-Study terminated because number of enrolled individuals after 5 years was still below necessary estimated sample size	[184]
Meltzer *et al.* (2003)	Multicenter, RCT, international, clozapine vs. olanzapine, n = 980 schizophrenia or schizoaffective disorder, 2 yrs	Suicide attempts/completion; hospitalizations to prevent suicide; rating of “much worsening of suicidality” from baseline; CGI-SS	Clozapine therapy was superior to olanzapine therapy in preventing suicide attempts in patients with schizophrenia and schizoaffective disorder at high risk for suicide	[99]
Verkes *et al.* (1998)	DB, RCT, paroxetine (40 mg/day) vs. placebo in 91 patients who had recently attempted suicide for at least a second time, 1 yr	Suicide attempt; self-rating scales for depressive symptoms, anger; Axis II diagnoses	With adjustment for the number of previous suicide attempts, paroxetine showed significant efficacy in the prevention of recurrent suicidal behavior	[185]

Abbreviations:
Hx – history; Tx – treatment; MADRS - Montgomery-Asberg Depression Rating Scale; HDRS – Hamilton Rating Scale for Depression; QIDS – Quick Inventory of Depressive Symptomatology; DB – double blind; RCT – randomized controlled trial; MDD – major depressive disorder; BD – bipolar disorder; SI – suicidal ideation; SSRI – selective serotonin reuptake inihibitor; IPT – interpersonal therapy; SSI - scale for suicide ideation; S-STS - Sheehan-Suicidality Tracking Scale; C-SSRS - Columbia Suicide Severity Rating Scale; SIS – Suicide Intent Scale; SUPLI - Suicide Prevention by Lithium - the Lithium Intervention Study; CGI-SS- Clinical Global Impression of Suicide Severity

Table 5

Clinical compounds implicating molecular targets for suicidal behavior.

Drug compound	Target	Clinical findings	Citations
Lithium	cAMP mediated signal transduction; CREB activation; BDNF; PI cascade; PKC inhibition; GSK-3 inhibition; Bcl-2 expression	Mood stabilizing and anti-depressant effects; thought to also target impulsivity and aggression (oral formulation)	[94,186]
Ketamine	mTOR; eEF2; BDNF; Arc; GSK-3 inhibition	Rapid antidepressant and antisuicidal effects (IV)	[111,112]
TRH	HPT axis	Rapid antidepressant effect (IV) and antisuicidal effects (IT)	[114,187]
Scopolamine	Muscarinic receptors; NMDA receptor expression; mTOR	Rapid antidepressant effects (IV); sub-analysis with suicide item score decreased in clinical rating scales	[188,189]
Allopurinol	Purinergic system	Shown to have efficacy in bipolar mania; may reduce impulsivity associated with suicidal behavior	[190,191]

Abbreviations:

cAMP: cyclic adenosine monophosphate; CREB: cAMP response element binding protein; BDNF: brain-derived neurotrophic factor; PI: phosphatidylinositide; PKC: protein kinase C; GSK-3: glycogen synthase kinase 3; Bcl-2: B-cell lymphoma 2; eEF2: eukaryotic elongation factor; TRH: thyrotropin releasing hormone; Arc: activity-regulated cytoskeletal associated protein; HPT: hypothalamic pituitary axis; NMDA: N-methyl-D-aspartate; IV: intravenous; IT: intrathecal; mTOR: mammalian target of rapamycin.