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Psychopharmacological Agents and Suicide Risk Reduction: Ketamine and Other Approaches

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Abstract Suicide is a major global public health problem and the leading cause of injury mortality in the USA. Suicide is a complex phenomenon involving several systems and neurobiological pathways, with interacting genetic and environmental mechanisms. The literature on the neurobiology and pharmacotherapy of suicide has been limited. To date, no medications have proven efficacious for treating acute suicidal crises. There is an emerging literature supporting a rapid anti-suicidal effect of ketamine, a non-competitive *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist, among depressed patients with suicidal ideation. Potential ketamine's anti-suicidal effect mechanisms are linked to interruption of the kynurenine pathway and modulating pro-inflammatory cytokines exacerbation. However, available data are not sufficient for its routine integration in clinical practice, and larger and replicated randomized control studies are needed.

Keywords Suicide · Ketamine · Depression · Pharmacotherapy · NMDA receptor

Introduction

The World Health Organization estimates that 1.5 million people will die by suicide in 2020 [1]. With more than 36,000 deaths per year, suicide is the leading cause of injury mortality in the USA [2, 3]. Approximately, 90 % of individuals who die by suicide have a history of mental illnesses [4]. Most of the suicide literature is epidemiological, and focuses on identification of risk factors. There are very few evidence-based approaches for prevention and even fewer randomized clinical trials for potential treatments. Cognitive behavioral therapy and [5] dialectical behavioral psychotherapy [6] studies provide growing evidence in suicide prevention among specific subgroups of patients with mental illness. Pharmacological approaches for the treatment and prevention of suicide rely mostly on the treatment of the primary psychiatric disorders and comorbid illnesses. To date, no medications have proven efficacious for treating acute suicidal crises. While lithium (Li) has the most encouraging data on reducing suicide among patients with mood disorders, clozapine has the Food and Drug Administration (FDA) indication for reducing the risk of recurrent suicidal behaviors in patients with schizophrenia or schizoaffective disorder.

There is an emerging literature supporting a rapid anti-suicidal effect of ketamine, a non-competitive *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist, among depressed patients with suicidal ideation. In this article, we briefly review the data on somatic treatments for suicidality, provide an overview of the basic and clinical pharmacology of ketamine, and conclude with a consideration of ketamine's emerging anti-suicidal data.

Somatic Treatments for Suicide

The potential role of medication in suicide prevention continues to be underestimated, and the evidence for the use of pharmacological interventions specifically to address suicide risk is limited [7]. A medication with an anti-suicidal property is one that can ameliorate acute or chronic suicidal behavior, as opposed to medications with nonspecific effects, such as sedating or anti-anxiety medications that can indirectly alter behavior.

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Clozapine

In 2002, the FDA approved clozapine for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder based on the findings from the International Suicide Prevention Trial [8]. Nine hundred fifty-six patients with schizophrenia or schizoaffective disorder classified as high risk for suicide due to previous suicide attempts or current suicidal ideations were randomized to receive either clozapine (dose range 200–900 mg/day) or olanzapine (dose range 5–20 mg/day). At the end of the 2-year study period, and compared to those on olanzapine, patients on clozapine had significantly fewer suicide attempts (34 vs 55; P=0.03), suicide attempt hospitalization (82 vs 107; P=0.05), rescue interventions to prevent suicide (118 vs 155; P=0.01), and concomitant treatment with antidepressants (221 vs 258; P=0.01) or anxiolytics (301 vs 331; P=0.03) [8]. In a meta-analysis, Hennen and Baldessarini reported that the relative risk for completed suicide was 2.9 times less with clozapine as compared with other treatments [9].

Lithium

Lithium (Li) is FDA-approved for treating acute mania and preventing recurrent mood episodes in patients with bipolar disorder. Lithium is also effective as an augmentation strategy in treatment-resistant depression and in relapse prevention in major depressive disorder [10–13]. The 2003 American Psychiatric Association (APA) Practice Guidelines for the assessment and treatment of patients with suicidal behavior stated that long-term use of Li is associated with major reductions in the risk of suicide and suicide attempt in patients with bipolar disorder and major depression [14]. The 2013 Veterans Health Administration/Department of Defense (VA/DoD) clinical practice guidelines for assessment and management of patients at risk for suicide states that "providers should consider treating patients with a unipolar depressive disorder with lithium in an effort to reduce the risk of suicide" [7]. Based on observational studies and meta-analyses for suicide and the prevention of suicide attempts, the effect sizes were largest in depression. In a 2013 review, Cipriani et al. reported that among patients with unipolar depression, Li reduced risk of death by suicide (OR=0.13, 95 % CI 0.02–0.76) and by all causes (OR=0.36, 95 % CI 0.13–0.98) [15•], yet there was no significant risk reduction in deliberate self-harm (OR=0.6, 95 % CI 0.27–1.32). Compared to placebo, Li decreased suicide risk 4–5-fold [16].

Antidepressants

In a recent meta-analysis of 372 double-blind randomized controlled trials, comprised of 99,231 subjects, Filaković and Erić found that antidepressants lowered the risk of suicide among treated patients compared to those on placebo [17•]. In unipolar depression, tricyclic antidepressants may have a protective effect against suicide [18]. Barbui et al. found that selective serotonin reuptake inhibitors (SSRIs) decreased suicide risk and behavior in their meta-analysis from 200,000 subjects [19]. Fluoxetine, the most studied SSRI, was reported to reduce anger [20], self-injurious behavior, and impulsive aggression [21–24]. Fluoxetine's anti-suicidal effect was noted in patients with OCD [25], anxiety [26], and bulimia [27]. A Cochrane review by Hawton et al. found that in comparison to placebo, antidepressants decreased odds of deliberate self-harm in patients with treatment-resistant depression (TRD) (OR=0.83, 95 % CI 0.47–1.48) [28].

However, the role of antidepressants, specifically SSRIs, in reducing suicide risk was questioned after the 2004 FDA warning that antidepressants increase suicide risk among children and adolescents, mostly early in treatment. Antidepressant-related increase in suicide risk is possibly related to treatment-emergent insomnia, agitation, akathisia, activated/mixed depression in latent bipolarity, and delayed onset of action of antidepressants. However, the same FDA data showed a protective effect of antidepressants against new onset or worsening of suicidal ideation [29]. The risk of suicide attempt in the antidepressant treated group was 1/3 that of the untreated group [30]. Patients reporting suicidal ideation or history of suicide attempts are more likely to be started on antidepressants. Active suicidal ideations and history of suicide attempts are risk factors for future suicidal behavior. Accordingly, antidepressant treatment is an outcome of suicidal behavior rather than the opposite. Practice guidelines continue to support the use of antidepressants, in all age populations, for the treatment of depression with or without suicide risk [7, 14].

Electroconvulsive Therapy

A new report by Fink et al. looked at the effect of electroconvulsive therapy (ECT) on suicide prevention based on studies by the Consortium for Research in ECT (CORE) [31•]. A total of 131 patients were identified as high acute suicide risk, based on a HAMD-24 suicide item score of 3 (having active suicidal thoughts) or 4 (reporting a suicidal event during the current episode). Progressive resolution of suicidal ideation was noted throughout the ECT course. The cumulative percentage of patients reporting an HRSD-24 suicide item score of 0 was 15.3, 38.2, 61.1, and 76.3 % after 1, 3, 6, and 9 ECT sessions, respectively. ECT undoubtedly remains the gold standard of treatment for suicidal depression; however, its rapidity of onset for elimination of suicidal cognitions may not be optimal. Nor are there strong data to document maintenance of suicide risk reduction following discontinuation of ECT treatments.

Ketamine

Ketamine Pharmacodynamics/Pharmacokinetics

Ketamine, a *N*-nethyl-D-aspartate (NMDA) glutamate receptor antagonist, was approved by the FDA in 1970 as an anesthetic agent. The elimination half-life is estimated to be 2–2.5 h. It is metabolized to norketamine and dehydronorketamine through the cytochrome P450 system, specifically CYP2B6, CYP3A4, and to a lesser extent CYP2C9. Ketamine has a complex pharmacological profile with a variable affinity for numerous receptors. In addition to being an open-channel nonselective NMDA receptor antagonist, ketamine interacts with several receptors that include intracellular sigma receptors, opioid μ-receptors, serotonin 5-HT3 receptors, muscarinic receptors, α7-nicotinic acetylcholine receptor, and the serotonin, norepinephrine, and dopamine transporters [32–35]. In the USA, ketamine is most commonly administered as a 1:1 racemic mixture of (S) and (R) ketamine, although (S)-ketamine is approved as an anesthetic in several EU countries. (S)-ketamine has 3–4 times higher affinity to the phencyclidine PCP binding site of the NMDA receptor than (R)-ketamine [36], and potentially better tolerability profile than the R-isomer or racemic mixture [37]. Administration routes for ketamine include intravenous (IV), intramuscular (IM), intranasal (IN), epidural, subcutaneous, transdermal, intra-articular, sublingual, and oral, giving it a potential advantage over currently used psychotropic medications.

Ketamine Efficacy in TRD

Berman et al. were the first to report on the rapid antidepressant effect of ketamine in 2000 [38]. In this early report, four of eight patients demonstrated a 50 % or greater reduction in HRSD-24 scores at 72 h post-infusion. A subsequent larger replication study by Zarate et al. using a cross-over design found that of the 17 subjects receiving ketamine, 12 (71 %), 8 (47 %), 6 (35 %), and 2 (12 %) met the response criteria at 24 h, 72 h, 1 week, and 2 weeks post-ketamine infusion, respectively [39]. Despite the very encouraging results of these two studies, they included a fairly small number of patients and used a cross-over design with an inert placebo. Our group recently conducted a parallel-arm, randomized, controlled trial of 72 patients with TRD randomized to ketamine (0.5 mg/kg over 40 min) or midazolam, a benzodiazepine anesthetic agent, under triple-masked conditions (patient, rater, anesthesiologist blind to treatment) [40••]. Patients in the ketamine group had significantly greater improvement in the Montgomery–Åsberg Depression Rating Scale (MADRS) score at 24 h compared to the midazolam group [$t(68)=3.34$, $P<0.001$]. After adjusting for baseline scores and site, ketamine improved MADRS score by 7.95 points compared to midazolam (95 % CI 3.20–12.71), corresponding to a large effect size (Cohen's $d=0.81$). Ketamine also increased the likelihood of response at 24 h compared to midazolam OR=2.18, 95 % CI 1.21–4.14, $P<0.006$). Our results provided further evidence supporting ketamine as a novel option for patients with TRD.

Ketamine and Suicide Risk Reduction

Recent literature supports the anti-suicidal effect of ketamine. A recent double-blind RCT confirmed initial case reports and open-label studies, demonstrating that ketamine may have a rapid anti-suicidal effect. These studies are summarized in Table 1 [41–48].

DiazGranados et al. reported on the immediate effect of ketamine on suicidal ideation [45]. Thirty-three patients with TRD received an open-label single infusion of ketamine (0.5 mg/kg over 40 min) followed by a blinded randomization to riluzole or placebo 6 h later. Based on baseline scores of the Scale for Suicidal Ideation (SSI), patients were classified as with (SSI≥4; $n=10$) or without (SSI≤3; $n=13$) significant suicidal ideation. At the end of the 40-min ketamine infusion, there was a marked improvement in SSI scores ($F=7.03$, df= 4.97, $P<0.001$), as well as the suicide items of the Hamilton Rating Scale for Depression (HRSD) ($F=17.25$, df=4106,

Table 1 Studies addressing ketamine and suicidality

Study	Study design[a]	Sample size	Diagnosis[a]	Regimen
Price et al. 2014 [41]	RCT	57	TRD	Single infusion of IV KET (0.5 mg/kg) vs. IV MID (0.045 mg/kg)
Zarate et al. 2012 [42]	RCT	15	Bipolar depression	A single infusion of IV ketamine (0.5 mg/kg) vs. Saline
Thakurta et al. 2012 [43]	OL	27	TRD	A single infusion of IV ketamine (0.5 mg/kg)
Larkin and Beautrais 2011 [44]	OL	14	MDD with SI	A single infusion of IV ketamine (0.2 mg/kg)
DiazGranados et al. 2010 [45]	OL	36	TRD	A single infusion of IV ketamine (0.5 mg/kg)
Price et al. 2009 [46]	OL	26	TRD	Six infusions of IV ketamine (0.5 mg/kg),
De Gioannis and De Leo 2014 [47]	CR	2	Bipolar depression	1.5–3 mg/kg PO KET every 2–4 weeks
Zigman and Blier 2013 [48]	CR	1	TRD	A single infusion of IV ketamine (0.5 mg/kg) + Li 600 mg

[a] *RCT* randomized controlled trial, *OL* open label, *CR* case report, *TRD* treatment-resistant depression, *MDD* major depressive disorder, *SI* suicidal ideation

$P<0.001$), the MADRS ($F=27.68$, df=4110, $P<0.001$), and the Beck Depression Inventory (BDI) ($F=5.82$, df=4103, $P<0.001$). The effect was very large at 40 min ($d=1.05$, 95 % CI 0.65–1.45), and moderate at 230 min ($d=0.45$, 95 % CI 0.12–0.77). By the end of the 40-min ketamine infusion, only one of the ten patients continued to have significant suicidal ideation. By 80 min, no participants met scores for suicidal ideation. The average time needed to achieve a score of zero on the SSI was 44 min (SE=4).

DiazGranados' findings were replicated in a report by Thakurta et al., of 27 patients with TRD receiving open-label ketamine (0.5 mg/kg) infusions over 40 min. The mean SSI scores of study subjects decreased by 4 points from a baseline average of 4.85 (SD=5.37) to a 40-min average of 0.78 (SD=1.48), ($P=0.001$). Ketamine's anti-suicidal effect persisted at 230 min post-infusion; however, mean SSI scores returned to baseline range at 24 and 48 h post-infusions [43].

Similar findings were reported in a double-blind, randomized, two-phase cross-over study (single IV ketamine 0.5 mg/kg infusion vs. saline) among 15 patients with bipolar depression [42]. The interaction between drug and time was significant for the suicide items of the MADRS [$F(9, 130)=4.68$, $P<0.001$], HDRS [$F(9163)=1.94$. $P=0.04$], and BDI [$F(9165)=1.98$, $P=0.045$]. As with the previous studies, suicidal ideation scores were decreased by 40 min and up to 3 days post-ketamine infusion [42].

Price et al. reported an average decrease of 2.08 on the MADRS-suicide item 24-h post single infusion of IV ketamine (0.5 mg/kg) among 26 patients with TRD [$t(25)=6.42$, $P<0.001$; $d=1.37$] [46]. There was a similar effect in a subset of patients who received six ketamine injections (3/week over a 2-week period). Ketamine's anti-suicidal effect persisted through the repeated infusion phase with no patients achieving a MADRS-SI>2. On average, there was a 2.8 point decrease in MADRS-suicide item score 24-h after the first ketamine infusion [$t(9)=5.47$, $P<0.001$; $d=2.17$] and 2.9 points 4 h after the sixth and last infusion (day=12), which was 2.89 [$t(8)=5.12$; $P=0.001$; $d=2.42$].

Our group recently reported a triple-blind (subject, rater, and anesthesiologist) randomized control study, in which 57 patients with TRD were randomized in a 2:1 ratio to receive a single infusion of ketamine (0.50 mg/kg) or midazolam 0.045 mg/kg) [41]. Suicidality was assessed by several measures, including the Beck Scale for Suicide Ideation (BSS), QIDS-SR suicidality item (QIDS-SI), and MADRS suicidality item (MADRS-SI). A composite explicit suicidality index (SI composite) was computed by summing z-scores of these three scale items. Twenty-four hours post-infusion, 53 % of ketamine-treated patients scored zero on all suicide measures compared with 24 % of the midazolam group ($\chi^2=4.6$; $P=0.03$).

Finally, Larkin and Beautrais administered 0.2 mg/kg IV bolus to 14 patients who presented to the ER with suicidal ideation [44]. MADRS-SI scores decreased from a mean score of 3.9 (SEM 0.4) to 0.6 (0.2), 0.6 (0.2), 07 (.2), and 0.6 (0.1) at 40, 80, 120, and 240 min post-ketamine bolus infusion. The decrease in MADRS-SI scores were maintained at 7 [mean 0.8 (SEM=0.1) and 0 (0.2) respectively].

Ketamine and the Neurobiology of Suicide

The neurobiology of suicide is poorly understood. Most of the literatures focuses on potential involvement of the serotonergic system, HPA axis, and immune-inflammatory modulators. With recent data on the anti-suicidal effect of ketamine, there has been an increased focus on the role of the glutamatergic pathways in suicide.

The serotonergic system has been the most studied and linked to suicide risk whether directly or through its role in mood disorders or impulsivity and aggression. Low platelet and CSF levels of 5-HIAA have been documented in patients with a history of suicide attempts [49–51] and who are more likely to reattempt and/or die by suicide [52]. Abnormal dexamethasone suppression tests (DST) reflecting a deregulated HPA axis has been linked to suicide [53]. In a 15-year follow up study, Coryell and Schlesser reported that patients with abnormal DST have a 14-fold increase in likelihood of future suicide compared to those with normal DST tests (OR=14.3, Wald $\chi^2=5.6$, $P=0.02$) [54]. Finally, data from interferon-alpha and beta for the treatment of hepatitis C [55] and multiple sclerosis [56] provide further link between the immune system and suicide. Steiner et al. has reported brain microglia activation in postmortem studies of depressed patients who died by suicide [57]. Elevated levels of pro-inflammatory and inflammatory cytokines have been reported in patients with increased risk of suicide including Il-4, Il-3, Il-14 [58], IL-6 [59], and TNF-alpha [60].

High levels of quinolinic acid (QUIN), a tryptophan metabolite, have been linked to severe depression and suicide through the activation of the tryptophan–kynurenine pathway [61••, 62, 63]. While tryptophan is mostly known as a precursor of serotonin and melatonin, only 5 % of tryptophan is metabolized through this pathway. The majority of tryptophan is metabolized to kynurenine by indoleamine 2,3-dioxygenase (IDO) or tryptophan 2, 3-dioxygenase (TDO). Through two separate pathways, kynurenine is metabolized to either QUIN, a NMDA receptor agonist, or kynurenic acid (KYNA), an endogenous NMDA receptor antagonist [63].

Erhardt et al. [61••] compared 64 patients with a recent, violent or nonviolent suicide attempt with explicit intent to die by suicide. Compared to 36 healthy subjects, suicide attempters had a significantly high CSF level of QUIN (Student's t test, $t=-5.39$, df=93.88, $P<0.001$). QUIN CSF levels correlated positively with Suicide Intent Scale scores

(n=53, Spearman P=0.30, P=0.028), with a trend noted between higher QUIN CSF among patients with violent suicide attempts compared to those with nonviolent attempts. However, KNYA levels did not differ significantly between the study groups (Student's t test, t=0.429, df=93.70, P=0.67). The findings by Erhardt et al. linked suicide to a hyperglutamatergic state manifested by an elevated QUIN levels.

Abnormal glucocorticoids and cytokines—due to dysregulated HPA axis or immune system—favor tryptophan metabolism through the kynurenine pathway and preferentially the QUIN arm. QUIN itself activates leukotriene and prostaglandin production activating and maintaining an immune system even further. The end result is a significant shunting of tryptophan through the kynurenine pathway and a decrease in serotonin production [63].

As a NMDA receptor antagonist, ketamine is hypothesized to block QUIN effects. Ketamine's role in regulating immune system homoeostasis has been long reported [64]. Ketamine administration is associated with reduced levels of circulating TNF-α, Il-8 and IL-6 [65, 66], and IL-1β [67]. Interestingly, in the absence of an inflammatory stimulus, ketamine has no effect on cytokine production. Thus, ketamine suppresses pro-inflammatory cytokines but not anti-inflammatory ones, and in so prevents exaggerated inflammatory reactions [64]. In summary, ketamine's potential anti-suicidal mechanism is linked to interruption of the kynurenine pathway self-induction and directly or indirectly prevents pro-inflammatory cytokine exacerbation, regulating a hyper glutamatergic state and restoring normal serotonin levels (Fig. 1).

Limitation of Suicide Treatment Literature

Suicide is a complex phenomenon involving several systems and neurological pathways, with interacting genetic and environmental mechanisms. The apparent absence of suicidal behavior in animals further complicates efforts to understand the underlying mechanism. Although seen and documented in all psychiatric disorders, suicide and/or suicide ideations/behaviors are part of the diagnostic criteria for MDD, bipolar depression, and borderline personality disorder. Various investigators have questioned whether understanding suicide as a phenomenon that cuts across psychiatric disorders could hinder understanding of underlying mechanisms and their treatment, and there have been suggestions that suicide may be better viewed as a distinct syndrome or diagnostic entity [68, 69]. Considering the complexities of contributing mechanisms and the low base rate of suicide, considerably larger populations and standardized longitudinal measurements are required to resolve this issue.

It is crucial to be able to look critically at reported effects of treatments on suicide including ketamine. Interpretation of treatment effects on suicidal behavior is complicated by considerations of bias and of the safety of placebo-controlled studies. At least two kinds of potential bias exist. First, in randomized clinical trials where the primary outcome measure

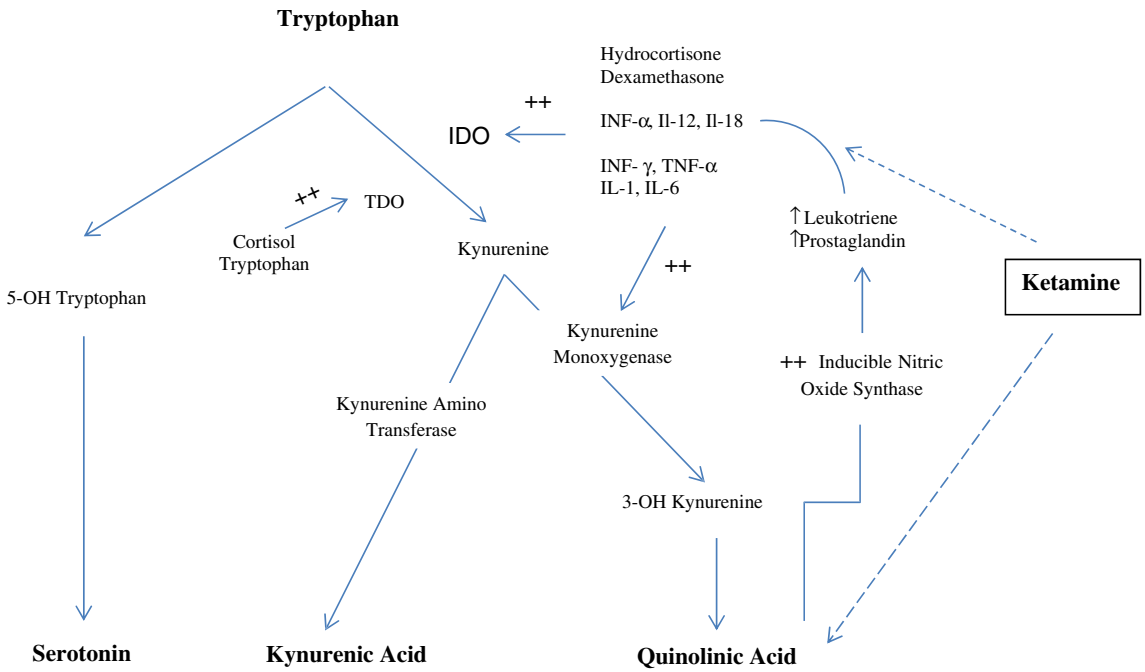

Fig. 1 Tryptophan metabolism and potential ketamine effect

Table 2 Open, active, interventional suicide studies registered on clinicaltrials.gov

Title	Clinical trial identifier	Study design	Intervention	Outcome measures	Study population
Ketamine for depression and suicide risk	NCT02094898	Open label	Repeated ketamine infusions	Improvement in depressive symptoms and suicide risk	18–65 year-old inpatient with TRD in unipolar or bipolar I/II inpatients
Lithium for suicidal behavior in mood disorders	NCT01928446	Double-blind RCT	Lithium vs. placebo	Time to the first repeated episode of suicidal behavior or hospitalizations for suicidality	Veterans with MDD or BD I or II + recent SA or inpatient tx to prevent suicide
Paroxetine/Bupropion in depression with suicide attempt or thoughts: fMRI study	NCT01748955	Double-blind RCT	Paroxetine CR vs. bupropion XL	SSI scores, fMRI changes	18–65 year-old with MDD + hx of SA or active SI
Lithium versus paroxetine in major depression	NCT01416220	Open-label RCT	Lithium vs. paroxetine	MADRS	>18 year old with MDD and family hx of suicide or BD
Ketamine for acute suicidal ideation in the emergency department: randomized controlled trial (LDK-SI)	NCT01892995	Double-blind RCT	Fluoxetine vs. diphenhydramine vs. placebo	BSSI	18–75 year old with SI
Ketamine in the treatment of suicidal depression	NCT01700829	Double-blind RCT	Ketamine vs. midazolam	Reduction of suicidal ideation	18–65 year old with MDD + SI
Reducing suicidal ideation through insomnia treatment (REST-IT)	NCT01689909	Double-blind RCT	Zolpidem-CR vs. placebo	Suicide Severity Index (SSI)	18–65 year old with MDD + SI and insomnia
Comparing treatments for self-injury and suicidal behavior in people with borderline personality disorder	NCT00834834	Single blind RCT	Fluoxetine vs. citalopram vs. DBT	Suicidal and self-injurious behavior	18–65 year old with BPD and current SI and hx of SA
A randomized, double-blind, placebo-controlled, sequential parallel study of CERC-301 in the adjunctive treatment of subjects with severe depression and recent active suicidal ideation despite antidepressant treatment	NCT01941043	Double-blind RCT	CERC-301 vs. placebo add-on to SSRI/SNRI	HDRS-17	18–70 year old with MDD + SI
Diclofenac add-on to treatment as usual for suicidal patients	NCT01413854	Double-blind RCT	Diclofenac vs. placebo	Suicide assessment scale scores	18–65 year old with depressive disorder and recent SA
Oral ketamine for suicidal ideation	NCT02037503	Double-blind RCT	Ketamine vs. placebo	Resolution of suicidal ideation	18–65 year old post SA requiring medical intervention among patients with or without TRD
Ketamine for suicidality in bipolar depression	NCT01944293	Double-blind RCT	Ketamine vs. midazolam	Beck scale for suicidal ideation	18–65 year old with bipolar depression and SI
Randomized, placebo-controlled multicenter trial of lithium plus treatment as usual (TAU) for acute suicidal ideation and behavior in patients with suicidal major depressive episode	NCT02039479	Double-blind RCT	Lithium vs. placebo	Sheehan Suicidality Tracking Scale	18>year-old inpatients with unipolar / bipolar depression with SI or SB
Ketamine for suicidal ideation	NCT01507181	Double-blind RCT	Ketamine vs. midazolam	Beck scale for suicidal ideation	18–80 year old inpatients with SI (excluding patients with psychotic disorders)

Table 2 (continued)

Title	Clinical trial identifier	Study design	Intervention	Outcome measures	Study population
A double-blind study to assess the efficacy and safety of intranasal Esketamine for the rapid reduction of the symptoms of major depressive disorder, including suicidal ideation, in participants who are assessed to be at imminent risk for suicide	NCT02133001	Double-blind RCT	Esketamine vs. placebo	Clinician's assessment of suicide risk based on suicide ideation and behavior assessment tool (SIBAT) MADRS	18–64 year old with MDD and imminent suicide risk
Treatment of suicidal ideation with intravenous ketamine infusion	NCT01887990	Double-blind RCT	Ketamine vs. placebo	BSSI	19–64 year old with SI excluding with BD or psychotic disorders
The better resiliency among veterans with omega-3's (BRAVO) study	NCT01901887	Double-blind RCT	W-3 fatty acid vs. placebo	New episode of significant suicide risk (NESSR)	18–90 year old veterans identified as high risk for suicide

is symptom reduction, suicidal patients are excluded. In addition, randomized clinical trials tend to exclude other patients who have comorbidities or complications of illness that might predispose to suicide [70]. Therefore, these studies arguably do not include the most relevant subjects for investigating risk of suicide, limiting their applicability. This may explain why rates of suicide mortality generally do not differ between subjects treated with placebo versus active drug in those with depressions [71, 72] or schizophrenia [73]. However, randomized, controlled trials addressing effects on suicidal behavior can be ethically and safely designed by using strategies including surrogate outcome measures, judicious use of rescue medicines, and psychosocial interventions including close monitoring [74]. The second type of bias applies to longer-term, more naturalistic studies comparing patients remaining on a treatment to those discontinuing it [75]. In this case, one must be aware of the potential confound of predictors of non-response to the treatment overlapping with risk for suicide, since individuals not responding to treatment would be more likely to stop taking the study medicine. Interestingly, one study demonstrated that patients not benefitting from the effects of lithium on relapse prevention still had lower rates of suicidal behavior [76]. Therefore, questions to consider in interpreting apparent treatment effects on suicidal behavior are as follows: (1) Was the study designed to investigate suicidal behavior? (2) Was the study designed in a manner deemed safe for potentially suicidal patients so as not to endanger them or bias against their participation? (3) Was the study designed in such a way where change in suicidal behavior could be directly linked to change in treatment exposure?

Conclusion

Literature on the neurobiology of suicide has been limited. Clozapine and lithium are two pharmacological interventions reported to reduce suicide risk. Ketamine may constitute an additional pharmacological treatment to counteract risk, and arguably it may represent a breakthrough approach because of its prompt actions for some. However, no published RCTs have examined its efficacy specifically for those in the highest-severity or risk groups.

A search on Clinicaltrials.gov for open, interventional suicide studies reveal a total of 85 studies (last accessed June 2014). Of those, 17 studies have suicide or suicidal behavior reduction as an outcome (Table 2). One placebo-controlled study is exploring the role of CERC-301, a selective NMDA receptor subunit 2B (NR2B), formerly known as MK-0657 among depressed patients with suicidal ideations. Ketamine is the interventional drug in seven studies (one open label, six double-blind RCTs of ketamine vs placebo, and three RCT of ketamine vs midazolam). While available data are not yet sufficient for routine integration of ketamine in

clinical practice, they are sufficient to call for larger and replicated randomized control studies.

Several future research directions for ketamine and "next-generation" NMDA receptor agents are essential: (1) testing these agents' specific anti-suicidal effects across diagnostic categories; (2) examination of the time course of anti-suicidal activity, to ensure that any acute benefits can be extended over a longer time period; and (3) developing a better understanding of biological mechanisms by which these agents confer protection against suicide. Regarding ketamine's mechanism of action, for example, recent discussion [77] has questioned whether ketamine's salutary impact on mood and suicidality might be derived primarily from its pharmacological activity at mu and kappa opiate receptor systems, rather than activity within the NMDA receptor channel. Further studies are indicated to explore these issues, with the public health goal of decreasing mortality and morbidity from suicide attempts and completed suicide.

Indoleamine 2,3-dioxygenase (IDO) or tryptophan 2,3-dioxygenase (TDO) inducers can shunt tryptophan through the kynurenine pathway instead of the serotonin one. TDO is induced by tryptophan and cortisol. IDO is induced by hydrocortisone, dexamethasone, TNF-G, TNF-a, INF-a, IL-1, IL-6, IL-12, and IL-18. Kynurenine monooxygenase activity is increased by INF-γ, TNF-α, IL-1, and IL-6 favoring quinolinic acid production. QUIA, a NMDA receptor agonist, is known to activate inducible nitric oxide synthase that leads to increase leukotriene and prostaglandin that potentiate an inflammatory response. Accordingly, a vicious cycle is created by an intertwined abnormality in the HPA axis and an unregulated immune response with increase in inflammatory and pro-inflammatory cytokine production which can further disturb the negative feedback inhibition of corticosteroids on the HPA axis. The end result is a significant shunting of tryptophan through the kynurenine pathway and a decrease in serotonin production. As a NMDA receptor antagonist, ketamine blocks QUIN effects and suppresses pro-inflammatory cytokines. Ketamine's potential anti-suicidal effect mechanisms are linked to interruption of the kynurenine pathway self-induction, and directly or indirectly prevent pro-inflammatory cytokines exacerbation, regulating a hyper glutamatergic state and restoring normal serotonin levels.

Compliance with Ethics Guidelines

Conflict of Interest Rayan K. Al Jurdi declares no conflict of interest.

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- • Of importance
- •• Of major importance

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