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Titrated Serial Ketamine Infusions Stop Outpatient Suicidality and Avert ER Visits and Hospitalizations

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ABSTRACT

Background: *Recent inpatient studies examining the effect of low-dose ketamine infusions in treatment resistant depression (TRD) have shown promising results in diminishing suicidal ideation (SI). We describe the efficacy of titrated serial ketamine infusions in stopping suicidal ideation and averting ER visits and hospitalizations in a large, naturalistic sample of adult and adolescent outpatients with TRD and complex psychiatric comorbidity in a real-world psychiatry outpatient practice.*

Methods: *This is a retrospective chart review of 231 adults and adolescents presenting with TRD and complex psychiatric comorbidity in a large real-world psychiatry office practice with > 5400 visits/year. Each patient underwent a 60-90 min comprehensive consultation by the single treating psychiatrist. Appropriate patients were treated with 6 serial, titrated ketamine infusions (0.5-1.2 mg/kg within 40-50 min) over 2-3 weeks. PHQ-9 was obtained at baseline and before each infusion. The presence, frequency, and intensity of suicidality expressed in PHQ-9 Item 9 was analyzed over the treatment course and correlated to decrease in total PHQ-9. Suicides, suicide attempts, ER visits and hospitalizations were analyzed over the course of treatment and for an additional 4 weeks.*

Results: *64% of TRD patients presented with SI. There were no suicides, attempts, ER visits or hospitalizations in this large real-world cohort. SI markedly diminished in 79%, and ceased completely in 59%. Remission of SI was progressive, occurring after 1 infusion in 36%; the remainder required 3.1 infusions and an average dose of 0.75mg/kg for remission of SI. Suicidal patients experienced higher rates of response and remission of TRD than non-suicidal patients.*

Conclusion: *This is the first report of serial titrated IV ketamine infusions in a real-world psychiatry office for adults and adolescents with TRD and complex psychiatric comorbidity to safely and rapidly treat severe suicidal ideation and avert suicide, ER evaluation and hospitalization. It represents the largest number of patients to date reported from a single site in studies of IV ketamine infusions for TRD and suicidality, and a potential breakthrough treatment option for psychiatrists to provide in the office.*

Keywords

Depression; Ketamine; Suicidal ideation; Suicide; Ketamine for suicidal ideation; Low dose ketamine infusions; Outpatient treatment for suicidal ideation; Real-world psychiatry practice; Psychiatric hospitalization; Serial ketamine infusions; Suicidality; Suicidal ideation treatment; Treatment resistant depression; TRD.

Introduction

There has been an explosion of interest in treating acute suicidal ideation (SI) in treatment resistant depression (TRD) [1] with ketamine [2-4], as well as esketamine [5] and other novel glutamate modulators [6] given the rising rates of suicide in the United States [7-9] and worldwide [10]. In the US, more than 9.4 million adults every year have serious thoughts about committing suicide [11,12], and hundreds of thousands seek treatment for suicidal ideation each year [13].

However, real-world [14] practical treatment for suicidal ideation in outpatients with treatment resistant depression is limited, and rapid, safe, effective treatments are urgently needed. Although

ECT remains the gold standard for treatment of TRD with SI, most outpatients will not consent to it due to risks of adverse side effects, and disruption due to driving and work restrictions related to adverse cognitive effects. There is only one medication in the US which is FDA approved for reducing suicidal behavior, clozapine, but only in patients with schizophrenia or schizoaffective disorder, and it works slowly [15]. Another, lithium, has independent protective effects in reducing suicidal ideation and suicidal behaviors, even in the absence of relief of depressive symptoms [16,17]. However, its use in outpatient settings for individuals with unipolar TRD is hampered by poor patient acceptance due to multiple potential side effects, burdensome laboratory monitoring and slow response due to the need for dose titration [18,19].

There is preliminary evidence suggesting that repetitive transcranial magnetic stimulation (rTMS) applied to the left dorsolateral prefrontal cortex may reduce suicidal ideation in inpatients where patients were intensively administered 9 treatments over 3 days [20]. A small study using accelerated theta-burst rTMS in suicidal patients with unipolar depression also found a decrease in suicidality but the difference was not statistically significant [21]. Another report which pooled data from two published studies found that bilateral TMS reduced SI compared to sham treatment [22].

Although the genesis of suicidal ideation and behaviors in any one individual is complex and multifactorial, it has been suggested that dysregulation in glutamate neurotransmission may underlie suicidal ideation [23-25], and to date, ketamine is the most widely studied glutamate modulator for the treatment of psychiatric disorders [26].

Intravenous ketamine infusions have emerged as fast-acting effective treatment for TRD and suicidal ideation in TRD. There are several studies dating back to 2006 [27] using single dose ketamine infusions for TRD which show a rapid response in depressive symptoms after a single infusion, in as little as 40 minutes, and lasting up to 7 days [28] or as long as 4 weeks in patients with a family history of alcohol-use disorder [29]. Feifel et al. showed that a single low-dose ketamine infusion is efficacious and well-tolerated in an academic clinical practice setting [14].

Serial ketamine infusion studies have mirrored these results [30-32] and extended the duration of response in adults [33-37] and adolescents [38]. In 2016, Cusin et al. showed that a two-step dose escalation of intravenous ketamine treated depression safely and effectively [39].

Recent studies have explored the response of acute and chronic suicidal ideation to IV ketamine infusions in varied settings. These studies have been conducted in controlled inpatient units [27], an emergency department in a military hospital [40], and in a general hospital where Kashani et al. reported significant reductions in the Scale for Suicidal Ideation (SSI) and the Montgomery Asberg Depression Rating Scale (MADRS) within 40-120 min following infusion [41], and Vulser et al. reported a single case in a general hospital of IV ketamine treating SI successfully [42].

Overall, the studies have been hampered by small numbers of enrolled patients, large drop-out rates of almost 50%, low single or repeat doses of ketamine, with only one published two-step dose escalation [39]. There are no published studies using serial dose titration.

Early studies [43-45] showed that suicidal ideation could respond to a single infusion of ketamine 0.5 mg/kg over 40 min with a suggestion that the response might only partially correlate to antidepressant response. There are reports with promising results for the treatment of suicidal ideation on inpatient units and among pooled patient populations from studies originally conducted for other purposes using a single low-dose ketamine infusion [46]. However, most of these studies excluded patients who were actively suicidal or who had made a recent suicide attempt.

In a randomized, midazolam-controlled trial of outpatients with chronic stable SI, Grunebaum et al. 2018 found that repeated, fixed dose ketamine infusions resulted in significant anti-suicidal effects within 24 hours with clinical improvement maintained for 6 weeks when combined with pharmacotherapy [47]. In contrast, in a two-step dose escalation study, Cusin et al. 2019 reported that ketamine was no better than placebo in the treatment of SI [39]. However, these findings were limited by a small sample size, high dropout rate and possible poor blinding. Notably, there are no published studies that evaluate whether serial IV ketamine infusions produces anti-suicide effects lasting longer than 6 weeks.

There is also substantial interest in studying IV infusions of ketamine and ketamine derivatives in acute and emergency settings for the rapid lysis of suicidal ideation and the potential for avoidance of suicidal behaviors [48,49]. These settings provide contained environments with around-the-clock staff monitoring for patients whose symptom severity requires this level of care. These patients voluntarily present to emergency room settings, are referred there by their clinicians, or brought by ambulance because there is no lesser level of care that could safely contain them with the level of suicidality they describe. Often this is because psychiatric treatments offered outside an acute inpatient setting usually require weeks of waiting for relief of depressive symptoms and relief of suicidal ideation. Indeed, antidepressants list emergence of suicidal ideation listed as a potential adverse effect, due to the risk of inducing agitation and/or mania. Agitation and akathisia are also very real, acute risks associated with the most common FDA-approved rapid augmentation treatments for major depression in the USA using atypical antipsychotics such as aripiprazole, brexpiprazole, and lurasidone.

Clinical use of ketamine for treatment resistant depression and other treatment resistant psychiatric disorders has far outpaced the available data and expert consensus [50] to guide treatment. The proliferation of pop-up clinics with non-psychiatrists offering intravenous, intramuscular, and oral ketamine for suicidal ideation, TRD and other treatment resistant psychiatric conditions has been

described as disturbing and potentially dangerous [51].

Individuals presenting for outpatient ketamine treatment with TRD are fragile, vulnerable, and extremely ill. Many are drawn by media reports that ketamine can silence suicidal ideation and make it stop. But data supporting the safe and effective use of IV ketamine infusions for rapid lysis of suicidal ideation in an outpatient psychiatric setting has been sparse [52,53]. In the largest meta-analysis to date of ketamine as a rapid treatment for suicidal ideation, which included 99 unique subjects pooled from 5 different studies, Bartoli et al. 2017 found that the effect of one ketamine infusion/bolus in reducing suicidal ideation within 4 hours was large, consistent and significant, but cautioned that their evidence should be considered "very low" due to limitations in trial study designs and possible publication bias [48].

We present the first report of the safe and effective use of serial, titrated IV ketamine infusions in a real-world outpatient psychiatry office practice for the rapid treatment of suicidal thoughts and imminent suicidality in a large group of adults and adolescents with treatment resistant depression and complex psychiatric comorbidity.

Materials and Methods

Data site

This is a large outpatient psychiatry practice (>5400 visits/year) staffed by one psychiatrist and one APRN, splitting the volume 80/20. The practice is located in a suburban area about 15 minutes from the state's capital, and 1.5-2.5 hours from Boston and New York, respectively and draws from a wide 4-state area nearby. There are 3 major hospitals located within 20 minutes of the office, all of which offer inpatient psychiatric beds, PHPs (partial hospital programs), and IOPs (intensive outpatient programs), and a specialty children's hospital located within 20 minutes which offers ER evaluation, inpatient psychiatric beds, and an extended care unit in the ER. The practice is a full-service psychiatric practice specializing in psychopharmacology and offering IV ketamine infusion evaluation and treatment, rTMS, psychotherapy, and MAT for opioid use disorders. A ketamine registry was established at the initiation of ketamine infusion services to collect demographic, treatment, outcome, and safety data.

Methods

We performed a retrospective chart review of 231 consecutive adults and adolescents (14-86) with TRD who presented for consultation to determine whether they might be appropriate candidates for treatment with IV ketamine.

Candidates underwent comprehensive diagnostic consultation lasting 60-90 minutes by a single psychiatrist. Medical, psychiatric, and psychotherapy records were requested for all patients from their treating providers (psychiatrist/ARPN, therapist, and PCP) before the first visit and reviewed when available. Procedures for obtaining and releasing medical records were HIPAA compliant, and written informed consent for records release was obtained from patients or their guardians. All adults gave written informed consent for off-label treatment. Adolescents were required to assent to treatment and required the assent of both parents and written informed consent by at least 1 accompanying parent. Written informed consent for all patients was obtained in accordance with the Declaration of Helsinki and in accordance with Hummingbird IRB Protocol #2019-55.

Extensive psychiatric history was obtained, including history of active and passive suicidal ideation, suicide attempts, ER visits for SI, psychiatric admissions, ECT, TMS, PHP/IOP programs, psychotherapy, and past and current comorbid psychiatric and medical conditions. History of psychopharmacology trials was detailed. During consultation, clinical assessment of suicide risk factors included access to or seeking lethal arms, alcohol and substance abuse, anxiety, agitation, recent loss, trauma, social isolation, talking about or posting about wanting to die, and hopelessness. Most patients presented on a variety of psychiatric medications managed by their outpatient psychiatrist/APRN, or in some cases, PCP, which were managed by their prescribing clinician throughout their ketamine treatment. All diagnoses were made at the first visit during consultation using DSM-V criteria.

Patients were screened with CLIA-waived 16-panel urine toxicology screens where appropriate, and referred for additional laboratory testing when clinically indicated.

Patients were excluded if they presented with active psychotic symptoms, a history of schizophrenia, poorly controlled arrhythmias or hypertension, interstitial cystitis or current UTI, and pregnancy.

All patients completed the 9-item Patient Health Questionnaire (PHQ-9) [54,55] on paper in the reception area at the first visit and immediately before each subsequent infusion in keeping with current standards of practice. Patients were instructed to complete the follow-up PHQ-9's to reflect symptoms since their last visit.

Patients were weighed at each visit, and reclined comfortably in quiet, private rooms on a leather chair or couch with warm blankets, dimmed lighting and the option of listening to their own soft music with eye shades. They were discouraged from use of visual stimuli, texting, or cell phone use. A family member or friend was permitted to remain in the treatment room during infusions.

Dosing and Titration

Racemic ketamine (50 mg/ml) was obtained from a variety of manufacturers, and the calculated dose was diluted to 20 ml with 0.9%NS and administered intravenously using a MedFusion 3500 syringe pump.

Appropriate patients were offered a series of six infusions of racemic ketamine scheduled over 2-3 weeks, with attempts to keep the infusion intervals to 4 days or less. The infusion series began with an initial dose of 0.5 mg/kg ketamine over 40 min. The dose was increased during the first infusion in increments of

0.1-0.2 mg/kg after 10 minutes if there was no evidence of end-gaze nystagmus, a decrease in verbal fluency, and dissociation by patient self-report and observation, to a max of 0.7 mg/kg. Dose titration at each subsequent visit in increments of 0.1-0.25 mg/kg was based upon physiologic and emotional tolerability of the prior infusion, patient self-report of improvement in SI and target symptoms, and decrease in PHQ-9 item 9 and total score, to a maximum of 1.2 mg/kg. Length of infusion was increased to 50 min if dissociative symptoms during any infusion were reported as too intense.

Management of side effects

Side effects were assessed by open-ended general inquiry and observation. Patients with a history of easy nausea, GI distress or vestibular dysfunction were offered ondansetron 4-8 mg IVP before each infusion. Side effects of nausea were managed with additional ondansetron 4 mg IVP during or after the infusion, or dimenhydrinate 25-50 mg po after the infusion.

Dissociation was anticipated and framed as a desirable indicator of treatment efficacy [55,56,58,59] rather than as an adverse event. Patients were carefully prepared to expect it with examples of dissociative symptoms before treatment began. Rare side effects of extreme anxiety or fear were managed by pausing or slowing the infusion and/or administration of midazolam 1-2 mg slow IVP.

Continuous monitoring

All patients were continuously monitored throughout each infusion for P, BP, R, 02% sat and cardiac waveform using Caretaker Medical, with continuous recording, wireless remote observation, and repeated nursing assessments during and after the infusion.

Safety precautions

The office is located 1500 feet (less than 2 minutes) from the local police/ambulance/EMT services. Emergency contact and notification procedures were in place in the event that a patient required ER referral or transport for evaluation of worsening suicidal ideation, intention, or planning. IV ketamine infusion treatment was provided to lyse suicidal ideation and treat persistent depressive symptoms as an alternative to acute ER referral, hospitalization, or ECT and in collaboration with the patients' treating clinicians.

Response

The PHQ-9 was presented and completed on paper in the reception area within 5 minutes before initial consultation and all subsequent infusion appointments. The presence, frequency, and intensity of Item 9 of the PHQ-9 was analyzed over the course of treatment and compared to overall decrease in total PHQ-9. Item 9 has been used as a brief screening measure for suicide risk. [54,55] Item 9 asks "How often have you been bothered by thoughts that you would be better off dead or of hurting yourself in some way?" and the item is scored as follow: "not at all" = 0, "several days" = 1, "more than half the days" = 2, and "nearly every day" = 3. It specifically evaluates the frequency of passive thoughts of death as a relief and active thoughts of suicide/self-harm within the past two weeks. It has been widely used as a single measure to assess the prevalence of suicidal ideation in research studies [55,60-63] Any response other than 0 is considered positive for possible suicide risk. Suicidal patients with responses other than 0 on Item 9 or with reported changes in Item 9 at any point were clinically assessed for suicide risk by the psychiatrist at the infusion appointment.

For suicidal patients, the paired t test and the Wilcoxon signed rank test were used to determine if the decrease in PHQ-9 Item 9 following the first infusion was significant. The Pearson's chi squared test with Yates' continuity correction was used to determine if suicidal or nonsuicidal status was correlated to depression response or remission on the PHQ-9.

Results

Demographic

In real-world settings, it is important to know the demographics of the area and of the practice as the cohort of patients presenting for ketamine consultation and treatment for TRD cannot be assumed to be similar to baseline practice demographics and composition.

Our real-word psychiatry office practice is a large psychopharmacology-based practice in a small suburban town of 26K. The practice has been in existence for more than 20 years with very high visibility and name recognition, despite increasing commercialization and packaging of psychiatric services by competing nearby hospitals. The practice has been fully fee-for-service for 20 years, although many nearby psychiatrists accept insurance reimbursement, and over the past 3 years, new independently practicing APRNs do the same. This is important to note because most insurers do not cover the cost of outpatient IV ketamine infusions for the treatment of TRD, suicidal ideation or any other psychiatric disorder. All patients paid for the cost of their treatment and were encouraged to submit superbills to their insurers for out-of-network reimbursement, which was routinely denied.

The practice (1 psychiatrist, 1 APRN) provided more than 5400 patient visits for ketamine infusions, TMS, psychopharmacology and psychotherapy in the year preceding this chart review, with 80% of visits by the psychiatrist and 20% of visits by the APRN who followed her own patients. Only 14% of patients in the practice come from the town of South Windsor, CT, which has 10K households and 2.6 people/household; the remainder come from cities and towns dispersed throughout the state and from a nearby 4-state area. Although the median income in the town is 93K, the three abutting small towns and cities have median incomes of 59K, 68K and 35K. In our current practice, our non-ketamine patients range in age from 13 to 89 with a median age of 43. 86.2% of patients are white, 9% are Asian, 4.6% are black, and 4.3% are Hispanic. 52% of patients are female.

Surprisingly, the demographics for TRD patients presenting for ketamine treatment and captured in this current study mirrored the general practice demographics, although many patients travelled quite a distance to come for treatment.

Illness Severity

This was a highly ill population of patients with treatment resistant depression (N=231, 79.22% unipolar depressive episode; 20.78% bipolar depressive episode). Demographics of the group of patients presenting with SI (N=133) are presented in Table 1.

Demographics		% (N=133)
Female		60.15% (80)
Male		39.85% (53)
Average Age		42.5 (range 14-81)
Ethnicity	Caucasian	96.99% (129)
	Asian	1.50% (2)
	African-American	0.75% (1)
	Hispanic	0.75% (1)
Marital Status	Single	63.91% (85)
	Married	26.32% (35)
	Divorced	12.78% (17)
	Widowed	2.26% (3)

Table 1: Demographics of Patients Presenting for Ketamine Treatment with Suicidal Ideation (N=133).

In our cohort of 231 patients, 12 patients were seen only once and were deemed not appropriate for treatment or did not return after their first visit. Analysis was performed on the remaining 219 patients. At presentation, 76.62% (N=177) of patients reported moderate to severe depressive symptoms with PHQ-9 >15, and 51.1% (N=118) were severely depressed with a PHQ-9 greater or equal to 20. Fully 60.73% (N=133) patients presented with suicidal ideation, and 39.73% (N=86) were nonsuicidal. Of the 133 suicidal patients, 8.27% (N=11) were adolescents less than 18 years old and 6.77% (N=9) were ages 65 and over.

Suicidal patients presented with more severe TRD symptoms, with a median PHQ-9 of 22 (mean 19.95) indicating severe depressive symptoms. Nonsuicidal patients, although meeting established criteria for TRD, were less symptomatic with a median PHQ-9 of 13 (mean 13.08) indicating only moderately severe depressive symptoms. The difference in median PHQ-9 at first visit between suicidal and nonsuicidal patient is significant and shows strong evidence of the difference in severity of illness in these two groups, both by lack of overlap of the means and of the confidence interval notches in the box plot (Figure 1).

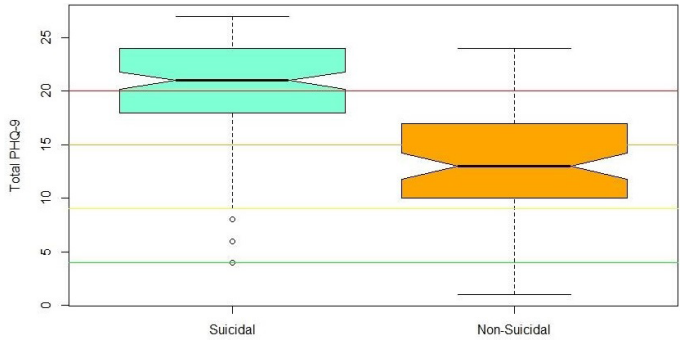

Figure 1: Comparison of Total PHQ-9 at First Visit for Suicidal vs. Nonsuicidal Patients (N=233).

Notably, 189 patients (86.30%) completed the entire series of 6 infusions; of the completers, 59.26% (N=112) were initially suicidal and 40.74% (N=77) were nonsuicidal.

Patients presenting for ketamine treatment had a high degree of psychiatric comorbidity and many patients had 3 or more concurrent psychiatric diagnoses. Although suicidal patients had more severe depressive symptoms than nonsuicidal patients, the range and frequency of concurrent psychiatric comorbidity among suicidal patients with TRD (N=133) was similar to the overall TRD cohort (N=219). 54% of suicidal patients with TRD had concurrent generalized anxiety disorder, 28% had OCD and 19% had concurrent panic disorder. PTSD and social anxiety disorder were each present in 15% of suicidal patients. There was also a high percentage of lifetime substance use disorders in 26% of suicidal patients (Figure 2).

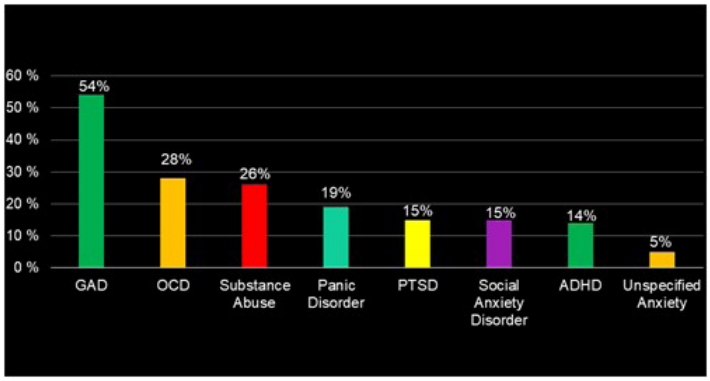

Figure 2: Comorbidity in Patients Presenting with Suicidal Ideation (N=133).

Suicidal patients (N=133) had a strong history of treatment failures and a high rate of previous psychiatric hospitalization and suicide attempts (Figure 3). More than 80% had failed at least 4 different antidepressants, not just two, more than half (53%) had been previously hospitalized psychiatrically, and 12% had made one or more previous suicide attempts. Many had a history of non-suicidal self injury. Notably, 12% had been previously treated with ECT and declined to consider it in the current episode due to treatment-failure or ECT-related cognitive dysfunction. 8% had previously failed a trial of rTMS.

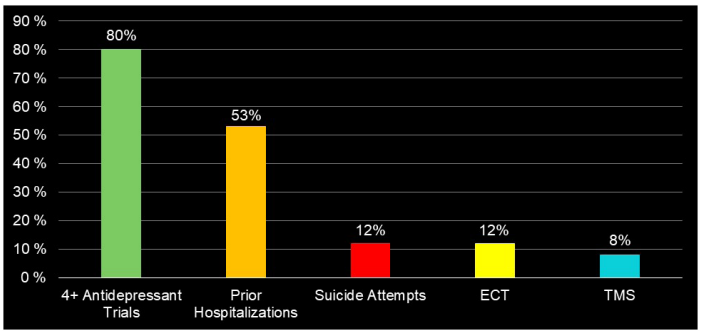

Figure 3: Previous Psychiatric History in Patients with Suicidal Ideation (SI).

Response and remission

Despite the severity of illness and the frequency and intensity of

SI in this large group of outpatients treated with serial titrated IV ketamine infusions (N=231), there were no suicide deaths, no suicide attempts, no ER visits and no psychiatric hospitalizations during the treatment period and for an additional 4 weeks.

78.94% (N=105) of all suicidal patients (N=133) had an overall decrease in SI by both objective and clinical measures; 58.64% (N=78) experienced complete cessation of SI and 20.30% (N=27) had reported much less frequent/intense suicidal thoughts. Remarkably, among suicidal patients with previous suicide attempts, 50.00% (N=13) experienced complete cessation of suicidal ideation. Suicidal ideation remained unchanged in 18.80% (N=25), and increased in 2.26% (N=3) (Figure 4).

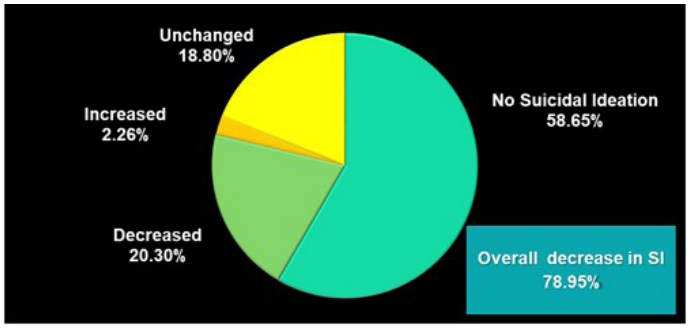

Figure 4: Change in Suicidal Ideation (SI) with Serial Titrated Infusions (N=133).

There was a direct and cumulative response of SI to serial titrated IV ketamine infusions (Figure 5). For suicidal patients (N=133), the drop in PHQ-9 Item 9 after the first infusion was significant under the significant level α=0.05 (using a parametric test, the paired t-test with p value 5.777x10-7, and a nonparametric test, the Wilcoxon signed rank test with p value 1.829 x 10^{-6}) (Figure 5). 35.62% (N=26) of all suicidal TRD patients (N=133) experienced complete cessation of SI after one infusion of 0.5 mg/kg over 40 min. Suicidality lifted with each subsequent infusion: an additional 21.92% (N=16) required 2 infusions for complete lysis of SI; 24.66% (N=18) required 3 infusions; 5.73% (N=5) required 4 infusions and 10.96% (N=8) required 5 infusions for complete cessation of SI. Figure 6 shows that the percentage of patients whose SI ceased (N=78) increased with serial titrated infusions.

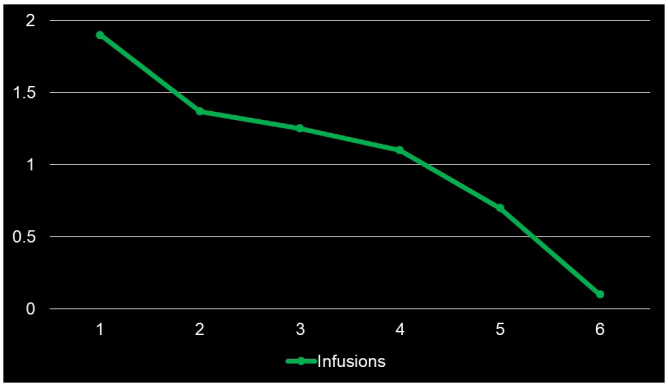

Figure 5: Change in Item 9 of PHQ-9 for Suicidal Patients.

Patients relieved of suicidal ideation after one infusion were slightly younger but much more ill than the overall TRD cohort: the average age was 40.5 years old; 88.5% had 4 or more antidepressant trials. More notably, 61.54% (N=16) of patients whose SI ceased after one infusion had a history of prior psychiatric hospitalization(s), and many had multiple hospitalizations; 50.00% (N=13) had made one or more prior suicide attempts, and 27% had made multiple suicide attempts; 3.85% had failed ECT and another 3.84% had failed TMS (Table 2).

Characteristics		% (N=26)
Female		62.53 (16)
Male		38.46 (10)
Average age		40.54 (range 19-74)
Marital Status	Single	46.15 (12)
	Married	34.62 (9)
	Divorced	15.38 (5)
Prior Hospitalization		61.54 (16)
Prior Suicide Attempt		50.00 (13)
Prior ECT		3.85 (2)
Prior TMS		3.84 (2)

Table 2: Characteristics of Patients Whose Suicidality Ceased After 1 Infusion.

Patients whose SI did not cease with one infusion required a total of 4.1 serial infusions for complete cessation of SI. In our cohort, 85.05% of all suicidal patients (N=133) who became suicide free (N=78) did so by the end of their 4th infusion, with the majority of patients experiencing remission of SI within the first 3 infusions (Figure 6).

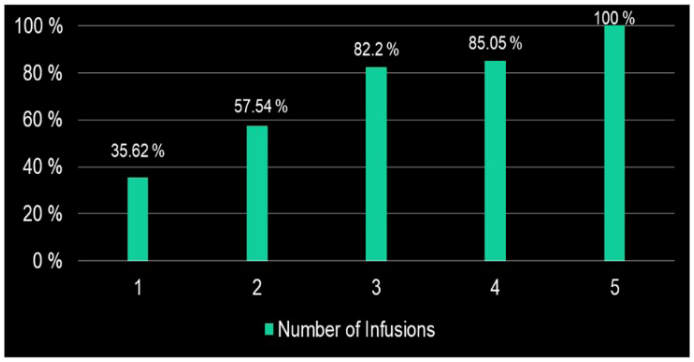

Figure 6: Number of Infusions Required to Stop Suicidality for Patients Whose SI Ceased Within the Course of 6 Infusions (N=73).

The average ketamine dose which stopped SI was 0.75 mg/kg over 40 min.

Notably, suicidal patients experienced high rates of response and remission of TRD symptoms. However, we found a marked decrease in suicidality even when patients remained quite depressed (Figure 7). The scatter plot shows the actual PHQ-9 scores for all suicidal patients whose SI ceased with ketamine, illustrating varied levels of depression were present when suicidal ideation first ceased during the treatment course.

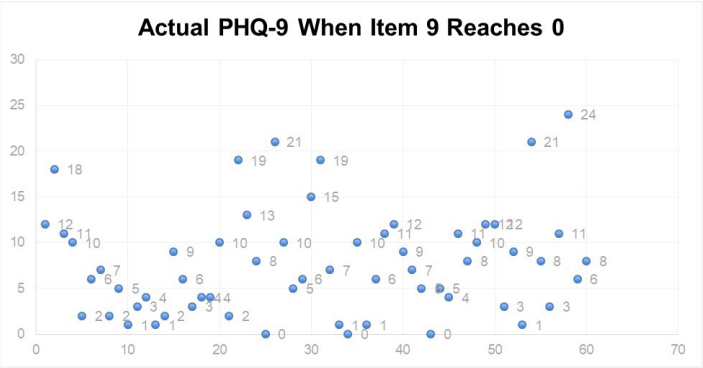

Figure 7: Actual PHQ-9 When Item-9 Reaches 0 (N=73).

As previously shown, reduction in SI was related to, but not fully explained by, improvement in depressive symptoms [64]. Suicidal patients who completed the course of 6 infusions (N=78) had dramatic reductions in PHQ-9 with a mean reduction of 19 and skewed in favor of many patients dropping 20 or more points (Figure 8). Nonsuicidal patients who completed the course of 6 treatments (N=86), beginning with a lower mean PHQ-9 (Figure 1), showed a reduction in PHQ-9 over the course of 6 treatments of 13, without the skew and with a high number of patients (N=10) showing no change in PHQ-9 (Figure 9).

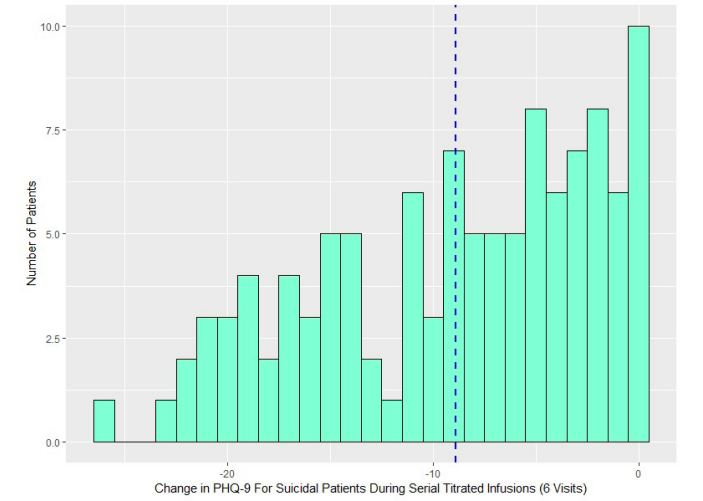

Figure 8: Change in PHQ-9 for Suicidal Patients During Treatment.

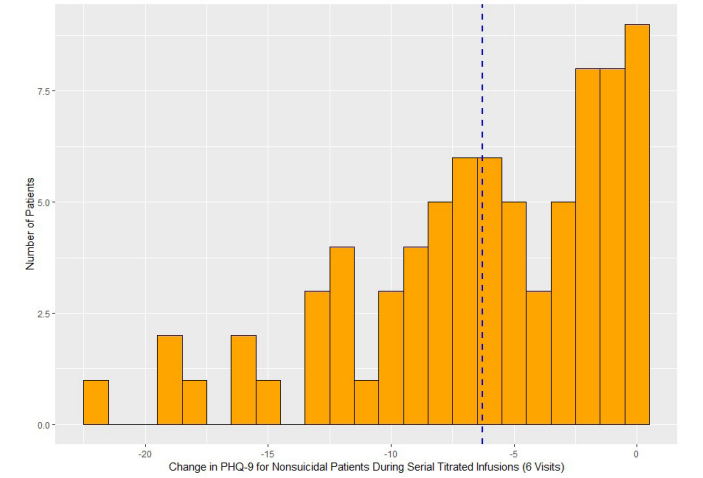

Figure 9: Change in PHQ-9 for Nonsuicidal Patients During Treatment.

Adverse effects

Dissociation was considered to be a marker of treatment efficacy, as mentioned earlier, not an adverse effect (AE), and was present in all patients. The most common AEs of ketamine during infusions were nausea, paresthesias, and blurred vision. Continuous VS monitoring revealed mild asymptomatic increases in P and BP which did not require active management. The most common AEs immediately following infusion were nausea, vomiting, and dizziness, which resolved quickly or responded to intervention. Rare AEs included drowsiness and headache which persisted for 24 hours and occurred in 2 patients. One patient experienced coughing after the infusion began, indicating possible mild laryngospasm, which resulted in treatment discontinuation.

Discussion

First report in a real-world psychiatry office practice

This is the first report of the use of serial IV ketamine infusions in a real-world psychiatry office for adults and adolescents with TRD and complex psychiatric comorbidity to safely and rapidly treat severe suicidal ideation and avert suicide deaths, suicide attempts, ER evaluation, and psychiatric hospitalization. It represents the largest number of patients to date (N=231) reported from a single site in studies of serial intravenous ketamine infusions for TRD and suicidality, and a breakthrough treatment option for psychiatrists to provide in the office.

Serial titrated ketamine infusions offer an effective, rapid, and safe opportunity for the treatment of acute suicidal ideation for selected outpatients in the safety and privacy of an outpatient psychiatry office, and afford an opportunity to avoid prolonged and costly ER evaluation and/or psychiatric hospitalization. IV ketamine offers a potentially life-saving breakthrough treatment for psychiatrists in office settings confronted with acute suicidal ideation or imminent suicidal risk in patients with TRD who wish to avoid, or who decline, hospitalization and are not committable, yet seek relief and remission from their SI and immediate reduction of risk.

This patient population of adults and adolescents is the most challenging to treat because of the acuity and high risk, and options for how and where to provide the most effective and safe treatment to actually reduce suicide risk and stop suicidal thoughts are limited.

Significance of response to ketamine treatment

The data is significant in several respects.

It is a true representation of real-world patients seeking ketamine infusion treatment for TRD, despite its lack of FDA approval for this indication. This large group consisted of patients who were quite ill with long histories of pharmacologic treatment failures, and the suicidal patients were significantly more depressed than non-suicidal patients.

What is extraordinary is that despite having extensive and complex

histories of previous suicide attempts, hospitalization, failed trials of more than 4 antidepressants, treatment failures with ECT and TMS, extensive psychiatric comorbidity and complex ongoing pharmacologic treatment with a variety of medications, the majority of these TRD patients were extraordinarily responsive to serial titrated ketamine infusions. Not only did many experience complete cessation of suicidal ideation within as little as 1 treatment, but for those whose SI did not remit with 1 infusion, serial titrated ketamine infusions yielded significant reduction in suicidality in more than 78.95% of patients and complete cessation of suicidal thoughts in 58.65%. For those whose SI did not cease following one 40 min infusion of 0.5 mg/kg, it required a total of 4.1 infusions and an average dose of 0.75 mg/kg IV ketamine over 40 minutes for complete cessation of suicidal thoughts. By the 4th infusion, 85.05% of our patients were free of suicidal thoughts.

Notably, even patients who were suicidal, high risk and more severely ill with TRD symptoms and high Item 9 scores experienced lysis of SI after 1 infusion. Among our patients whose suicidality ceased after 1 infusion (N=26), 62.54% (N=16) had been previously hospitalized and 50% had made prior suicide attempts.

More importantly, although many of the suicidal patients in this cohort were self-referred for SI or referred by their clinicians as a "last ditch effort" before heading to the ER or hospital, no patients in this cohort died by suicide, made a suicide attempt, or required ER evaluation or inpatient psychiatric hospitalization during their course of treatment or in the 4 weeks following treatment as they transitioned back to the care of their private clinicians.

Significance of the findings

This study was undertaken with the mix of both acute and, for some, chronic suicidal ideation, intention, and planning that is seen in outpatients with severe and moderately severe treatment-resistant depression. Due to a lack of rapid psychopharmacologic options for acute suicidal ideation and imminent suicide risk, many of the patients in this cohort might have been referred to the ER by their treating psychiatrists had they presented to their offices rather than ours and many had a history of multiple ER visits for SI occurring in just that context, or after actual suicide attempts. Most of the suicidal patients had severe psychiatric comorbidity highly associated with agitation, which is one of the key risk factors for imminent suicide—more than 20% had bipolar disorder and a majority of the others had severe anxiety disorders associated with increased suicide risk.

The lack of available rapid outpatient treatment options other than ECT for suicidal ideation in patients with severe depression and comorbid psychiatric disorders highly associated with agitated states exerts an extremely high burden for these patients financially, in quality of life, and in survival. In many areas, referrals for ECT are often delayed by days or weeks due to requirements for a complete physical and ECG by the ECT service before consultation is scheduled and further delayed until ECT can be scheduled for administration.

This suggests that having a rapid, safe, and effective treatment to offer outpatients with suicidal ideation in the context of TRD and complex psychiatric comorbidity -- coupled with data regarding the likelihood of relief of SI, expectations about how soon that relief of SI can occur and at what dose of ketamine -- may be critically life-saving. It offers these patients, their families, and their clinicians the opportunity for treatment before resorting to costly prolonged ER evaluation/holding and potentially costly hospitalization.

Limitations

This retrospective chart review was limited in several respects. The data arises from a single outpatient psychiatry practice site in a suburban area and the patient cohort is predominantly Caucasian, which may limit the generalizability of the findings. However, there is excellent validity and reliability in having a single psychiatrist extensively review outpatient treatment records and perform all of the comprehensive diagnostic evaluations and clinical follow up during infusion treatment compared to reports that pool patients from multiple sites with multiple raters.

The dose titration of ketamine was not scheduled or standardized, and depended upon tolerability, degree of dissociation, and patient response. In addition, the interval in between infusion treatments varied due to practical transportation needs as patients were not allowed to drive themselves home after infusions.

In addition, most of these patients were maintained on a variety of psychotropic medications, including antidepressants, mood stabilizers, antipsychotics, sleep agents, naltrexone, buprenorphine, and low dose varied benzodiazepines (< clonazepam 1 mg po qd or equivalent(s), when possible) which were managed by their outpatient clinicians. Many, but not all, received varied forms of psychotherapy throughout the infusion period. When possible, infusions were scheduled the day before psychotherapy. However, we did not control for the number or class of concurrent psychotropic medications or the frequency or type of psychotherapy during the treatment period.

The data is further limited by use of the PHQ-9 as the only formal rating instrument, but this accurately reflected current clinical practice at the time of data collection. The PHQ-9 is a valid outpatient self-administered scale for the assessment of depression severity [65-67]. Although it has not been validated for frequent follow-up in this patient population at intervals shorter than 2 weeks, it is widely used in outpatient psychiatric and primary care practices for follow-up with instructions commonly modified in practice to rate "since the last visit" if the visit interval is shorter than 2 weeks.

Given our clinical experience, suicidality was clinically assessed throughout treatment, although we relied on a single item from the PHQ-9 rather than a longer suicide-specific assessment for our analysis [68,55]. It is well known that self-reported SI on PHQ-9 Item-9 with any score greater than 0 in outpatients is a strong predictor of suicide attempt and a moderate predictor of

suicide death in the subsequent year [54]. The risk is low initially, increases over days and then continues for months throughout the subsequent year, with half of all attempts and suicide deaths occurring in patients who presented with Item 9 scores of "more than half the days" (score 2) or "nearly every day" (score 3) [54].

Item 9 has been compared against the C-SSRS in a large outpatient tertiary referral psychiatry clinic (>56,000 visits/year) [55] and both have been shown to have similarly high sensitivity of 95% in detecting possible suicide risk, although the specificity of suicidal risk for Item 9 was modest (76.8%) compared to C-SSRS (95.3%) and the positive predictive value of both scales was low (5.5% vs 22.4%). There is a high false-positive rate using only PHQ-9 Item 9 in non-psychiatric specific populations, e.g., primary care, systemic sclerosis, coronary artery disease, and cancer [60,69-71]. Since this paper was prepared, Item 9 of the PHQ-9 has been specifically validated against the C-SSRS in psychiatric patients. One recent small study found the PHQ-9 to be an insufficient assessment tool for suicidal thoughts and suicide risk [72]. Our conclusions may be limited by the lack of extensive suicide assessment rating scales for our cohort and absence of patient rating scales which could have more nimbly reported change in depressive symptoms. Again, this reflects real-world practice.

We might have obtained more robust data regarding wish to live and wish to die had we used the Scale for Suicide Ideation [73], the Columbia-Suicide Severity Rating Scale (C-SSRS) [74], the Suicide Status Form (SSF) [75], or the Concise Health Risk Tracking Scale (CHRT) for assessment of suicidality in depressed outpatients [76], and we have changed our clinical practice to include scales much more sensitive to interval changes in depressive symptoms and more comprehensive scales for suicidal ideation since this data was collected.

Life-Saving Intervention

One of the most critical responsibilities we undertake in psychiatry is the assessment of suicide risk, and there is widespread agreement through multiple studies and meta-analyses that despite widespread knowledge of risk factors, and warning signs of growing suicidal risk, suicide cannot be predicted. The number of lives lost to suicide continues to rise at an alarming rate despite initiatives to improve identification, assessment and outreach.

What has been missing is a rapid, safe treatment for acute suicidality and imminent suicidal risk that can offer selected outpatients immediate relief, an alternative to the ER or psychiatric hospitalization and potentially a reduced risk of suicide attempt and suicide death for the subsequent year [55].

We show compelling evidence that offering serial, titrated ketamine infusions to real-world suicidal outpatients with TRD, multiple comorbid conditions, risk factors for agitation, and suicidal ideation may be a safe, effective, and life-saving intervention which can stop suicidal ideation and avert ER and hospital admission -- and that this treatment can be effective even in patients who have previously attempted suicide, been hospitalized, failed ECT, and/or failed TMS.

It is important to recognize that the setting for this suicide treatment intervention is a psychiatric practice with seasoned clinicians and deep expertise in the treatment of the patients' underlying psychiatric disorders, not a free-standing ketamine clinic, and our results may not be generalizable to other settings. But in this very ill and high-risk suicidal cohort, no patient died by suicide, made a suicide attempt, or required ER evaluation/admission or psychiatric hospitalization. This is quite striking.

Clearly, more data is needed regarding the safety and efficacy of single and repeat-dose infusions and the safety, efficacy and optimal dosing strategies for serial, titrated intravenous ketamine infusions in the treatment of suicidality in TRD. More research is needed in the treatment of SI in other primary psychiatric conditions associated with agitated states and high suicide risk, across a variety of clinical settings – psychiatry office practices, hospital-based clinics, ER settings and inpatient units. And more data is needed regarding the potential adverse effects of short-term and long-term exposure to serial ketamine infusions and other forms of continued or intermittent ketamine treatment, at varied doses, particularly the risk of ketamine cystitis [77].

In addition, the results presented here need to be replicated with more detailed and sensitive instruments, and the response of suicidality to IV ketamine needs to be more carefully studied in larger outpatient groups, with controlled trials, diverse patient populations, controls for concurrent treatment with medications and psychotherapy, and analysis of the effect of comorbid psychiatric conditions. Carefully designed studies with serial titrations of ketamine are needed to verify the number of infusions required to stop suicidal thinking if it does not cease after one infusion, and to determine ideal dose increments, treatment frequency, and long-term side effects.

However, in the meantime, and in the real world, there is an urgent need for us to carefully consider the potential life-saving intervention available to us now in offering serial ketamine infusions to suicidal outpatients with TRD and other psychiatric comorbidity at imminent risk of suicide. The potential to avert suicide, preserve life, reduce patient and family suffering, and reduce healthcare costs is enormous.

Abbreviations

AE: Adverse Effect(s); APRN: Advanced Practice Registered Nurse; CLIA: Clinical Laboratory Improvement Amendments; CHRT: Concise Health Risk Track Scale (for assessment of suicidality in outpatients); C-SSRS: Columbia-Suicide Severity Rating Scale; ECT: Electroconvulsive Therapy; ER: Emergency Room/Emergency Department; IOP: Intensive Outpatient Program; IV: Intravenous; IVP: Intravenous Push; MADRS: Montgomery-Asberg Depression Rating Scale; MAT: Medication-Assisted Therapy; PHP: Partial Hospital Program; SI: Suicidal Ideation; SSF: Suicide Status Form; SSI: Scale for Suicide Ideation; PHQ-9: Physicians' Health Questionnaire-9; rTMS/TMS: Repetitive

Transcranial Magnetic Stimulation; TRD: Treatment Resistant Depression.

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References

1. Fava M. Diagnosis and definition of treatment-resistant depression. Biol Psychiatry. 2003; 53: 649-659.
2. Ahmed S, Hassan M, Venigalia H, et al. Ketamine's journey from sedation to suicide prevention: a viewpoint. J Psychiatry. 2016; 19: 383-384.
3. Price RB, Matthew SJ. Does ketamine have anti-suicidal properties? Current status and future directions. CNS Drugs. 2015; 2993: 181-188.
4. Ionescu DF, Bentley KH, Eikermann M, et al. Repeat-dose ketamine augmentation for treatment-resistant depression with chronic suicidal ideation: A randomized, double blind, placebo controlled trial. J Affect Disorders. 2019; 243: 516-524.
5. Canuso CM, Singh JB, Fedhchin M, et al. Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study. Am J Psychiatry. 2018; 175: 620-630.
6. Wilkinson SR, Sanacora G. A new generation of antidepressants: an update on the pharmaceutical pipeline for novel and rapid-acting therapeutics in mood disorders based on glutamate/GABA neurotransmitter systems. Drug Discovery Today. 2019; 24: 606-615.
7. Murray CJ, Atkinson C, Ghalla K, et al. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. JAMA. 2013; 310: 591-608.
8. Goldsmith SK, Pellmar TC, Kleinman AM, et al. Reducing suicide: a national imperative. The National Academies Press, Washington DC, USA, 2002.
9. Centers for Disease Control and Prevention. National Center for Health Statistics. Suicide rising across the US. https://www.cdc.gov/vitalsigns/suicide/index.html. Accessed 1/21/2019.
10. World Health Organization. Global Health Observatory Data. Suicide Rates per 100,000. https://www.who.int/gho/mental_health/suicide_rates/en/index2.html. Accessed 1/21/2019.
11. Crosby AE, Han B, Ortega LA, et al. Suicidal thoughts and behaviors among adults aged >/+ 18 years—United States 2008-2009. MMWR Surveill Summ. 2011; 60: 1-22.
12. Substance Abuse and Mental Health Service Administration. National Survey on Drug Use and Health Data Review. Suicidal Thoughts and behavior among adults: results from the 2014 National Survey on Drug Use and Health. 2015. https://www.samhsa.gov/data/sites/default/files/NSDUH-FRR2-2014/NSDUH-DR- FRR2-2014.htm. Accessed 2/16/2019.
13. Ting SA, Sullivan AF, Boudreaux ED, et al. Trends in US emergency department visits for attempted suicide and self-inflicted injury 1993-2008. Gen Hosp Psychiatry. 2012; 34: 5577-5565.
14. Feifel D, Malcolm B, Boggie D, et al. Low-dose ketamine for treatment resistant depression in an academic clinical practice setting. J Affect Disorders. 2017; 221: 283-288.
15. Meltzer HY, Alphs L, Green AI, et al. Clozapine treatment for suicidality in schizophrenia: International Suicide Preventional trial (InterSePT). Arch Gen Psychiatry. 2003; 60: 82-91.
16. Baldessarini RJ, Tondo L, Hennen J. Effects of lithium treatment and the discontinuation on suicidal behavior in bipolar manic-depressive disorders. J Clin Psychiatry. 1999; 60: 77-84.
17. Baldessarini RJ. Reducing suicide risk in psychiatric disorders. Curr Psychiatry. 2003; 2: 14-24.
18. Guzzetta F, Tondo L, Centorrino F, et al. Lithium treatment reduces suicide risk in recurrent major depressive disorder. J Clin Psychiatry. 2007; 68: 380-383.
19. Riesselman A, Johnson E, Palmer E. Lithium and clozapine in suicidality: shedding some light to get out of the dark. Mental Health Clin. 2015; 5: 237-243.
20. George MS, Raman R, Benedek DM, et al. A two-side pilot randomized 3 day trial of high dose left prefrontal repetitive transcranial magnetic stimulation (rTMS) for suicidal inpatients. Brain Stimulation. 2014; 7: 421-431.
21. Desmyter S, Duprat R, Baeken C, et al. The acute effects of accelerated repetitive transcranial magnetic stimulation on suicide risk in unipolar depression: preliminary results. Psychiatr Danub. 2014; 26: 48-52.
22. Weissman CR, Blumberger DM, Brown PE, et al. Bilateral repetitive transcranial magnetic stimulation decreases suicidality in adults with treatment resistant depression. Biological Psychiatry. 2017; 81; S331-S331.
23. Sanacora G, Treccani G, Popoli M. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. Neuropharmacology. 2012; 62: 63-77.
24. Bernstein HG, Tausch A, Wagner R, et al. Disruption of glutamate-glutamine-GABA cycle significantly impacts on suicidal behavior: survey of the literature and own findings on glutamine synthetase. CNS Neurol Disord Drug Targets. 2013; 12: 900-913.
25. Zhao J, Verwer RW, van Wamelen DJ, et al. Prefrontal changes in the glutamate-glutamine cycle and neuronal/glial glutamate transporters in depression with and without suicide. J Psychiatr Res. 2016; 82: 8-15.
26. Wilkinson ST, Sanacora G. A new generation of antidepressants: an update on the pharmaceutical pipeline for novel and rapid-acting therapeutics in mood disorders based on glutamate/GABA neurotransmitter systems. Drug Discovery Today. 2019; 24: 606-615.
27. Zarate CA Jr, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment- resistant major depression. Arch Gen Psychiatry. 2006; 63: 856-864.
28. Coyle CM, Laws KR. The use of ketamine as an

antidepressant: a systematic review and meta-analysis. Hum. Psychopharmacol. 2015: 30: 152-163.
29. Niciu MJ, Luckenbaugh DA, Ionnescu DF, et al. Ketamine's antidepressant efficacy is extended for at least four weeks in subjects with a family history of an alcohol use disorder. Int J Neuropsychopharmacol. 2015; 18: 1-7.
30. Diamond PR, Farmery AD, Atkinson S, et al. Ketamine infusions for treatment resistant depression: a series of 28 patients treated weekly or twice weekly in an ECT clinic. J Psychopharmacol. 2014; 28: 536-544.
31. Murrough JW, Perez AM, Pillemer S, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatry. 2013; 74: 250-256.
32. Singh JB, Fedgchin M, Daly EJ, et al. A double-blind, randomized placebo-controlled dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. Am J Psychiatry. 2016; 173: 816-826.
33. aan het Rot M, Collins KA, Murrough JW, et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. Biol Psychiatry. 2010; 67: 139-145.
34. Rasmussen K, Lineberry T, Galardy C, et al. Serial infusions of low-dose ketamine for major depression. J Psychopharm. 2013; 27: 444–450.
35. Virani S, Branch N, Albuquerque C, et al. Exploring the role of ketamine in maintaining the antidepressant response. Psychiatric Annals. 2018; 48: 437-446.
36. Messer M, Haller IV, Larson P, et al. The use of a series of ketamine infusions in two patients with treatment resistant depression. J Neuropsychiatry Clin Neurosci. 2010; 22: 442-444.
37. Szymkowicz SM, Finnegan N, Dale RM. A 12-month naturalistic observation of three patients receiving repeat intravenous ketamine infusions for their treatment-resistant depression. J Affective Disorders. 2013; 147: 416-420.
38. Cullen KR, Maatya P, Roback MG, et al. Intravenous ketamine for adolescents with treatment-resistant depression: an open-label study. J of Child and Adolescent Psychopharmacology. 2018; 28: 1-8.
39. Cusin C, Ionescu DF, Pavone KJ, et al. Ketamine augmentation for outpatients with treatment resistant depression: preliminary evidence for two-step intravenous dose escalation. Aust N Z J Psychiatry. 2016; 51: 55-65.
40. Burger J, Capobianco M, Lovern R, et al. A double- blinded, randomized, placebo-controlled sub-dissociative dose ketamine pilot study in the treatment of acute depression and suicidality in a military emergency department setting. Mil Med. 2016; 181: 1195-1119.
41. Kashani P, Yousefian S, Amini A, et al. The effect of intravenous ketamine in suicidal ideation of emergency department patients. Emerg (Tehran). 2014; 2: 36-39.
42. Vulser H, Vulser C, Rieutord M, et al. Ketamine use for suicidal ideation in the general hospital: case report and short review. Journal of Psychiatric Practice. 2018; 24: 56-59.
43. DiazGranados N, Ibrahim LA. Brutsche ND, et al. Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. J Clin Psychiatry. 2010; 7: 1605-1611.
44. Price RM, Iosifescu DV, Murrough JW, et al. Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. Depress Anxiety. 2014; 31: 335-343.
45. Price RB, Matthew SJ. Does ketamine have anti-suicidal properties? Current status and future directions. CNS Drugs. 2015; 29: 181-188.
46. Ballard E, Yarrington J, Farmer C, et al. Characterizing the course of suicidal ideation response to ketamine. J Affect Disord. 2018; 241: 86-93.
47. Grunebaum M. Ketamine for rapid reduction of suicidal thoughts in major depression: a midazolam-controlled randomized clinical trial. Am J Psychiatry. 2018; 175: 327-335.
48. Bartoli F, Riboldi I, Crocamo C, et al. Ketamine as a rapid-acting agent for suicidal ideation: a metanalysis. Neurosci and Biobehav Rev. 2017; 77: 232-236.
49. Charney DS, Matthew SJ, Manji HK, et al. Methods for treating suicidal ideation. United States Patent 9,439,220 B2. 2017-1-10.
50. Sanacora G, Frye MA, McDonald W, et al. American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments. A consensus statement on the use of ketamine in the treatment of mood disorders. JAMA Psychiatry. 2017; 74: 399-405.
51. Thielking M. Ketamine gives hope to patients with severe depression. But some clinics stray from the science and hype its benefits. https://www.statnews.com/2018/09/24/ketamine-clinics-severe-depression-treatment. 2018.
52. Rajkumar R, Fam J, Yeo EYM, et al. Ketamine and suicidal ideation in depression: jumping the gun? Pharmacol Res. 2015; 99: 23-35.
53. Reinstatler L, Youssef NA. Ketamine as a potential treatment for suicidal ideation: a systematic review of the literature Drugs R.D. 2015; 15: 37-43.
54. Simon GE, Rutter CM, Peterson D, et al: Do PHQ-9 Depression Questionnaires completed during outpatient visits predict subsequent suicide attempt or suicide death? Psychiatr Serv. 2013; 64: 1195-1202.
55. Viguera AC, Milano N, Ralston L, et al. Comparison of electronic screening for suicidal risk with the patient health questionnaire Item 9 and the Columbia Suicide Severity Rating Scale in an outpatient psychiatric clinic. Psychosomatics. 2015; 56: 460-469.
56. Krupitsky EM, Grinenko AY. Ketamine psychedelic therapy (KPT): a review of the results of ten years of research. J Psychoact. Drugs. 1997; 29: 165-183.
57. Niciu MJ, Shovestul BM, Jaso BA, et al. Features of dissociation differentially predict antidepressant response to ketamine in treatment-resistant depression. J Affect Disord. 2018; 232: 310-315.
58. Luckenbaugh DA, Niciu MJ, Ionescu DF, et al. Do the dissociative side effects of ketamine mediate its antidepressant

effects? J Affect Disord. 2014; 159: 56-61.
59. Pennybaker SJ, Niciu MJ, Luckenbaugh, et al. Symptomatology and predictors of antidepressant efficacy in extended responders to a single ketamine infusion. J Affective Disorders. 2017; 208: 560-566.
60. Bauer AM, Chan YF, Huang H, et al. Characteristics, management, and depression outcomes of primary care patients who endorse thoughts of death or suicide on the PHQ-9. J Gen Intern Med. 2013; 28: 363-369.
61. Denneson L, Corson K, Helmer D, et al. Mental health utilization of new- to-care Iraq and Afghanistan veterans following suicidal ideation assessment. Psychiatry Res. 2014; 217: 147-153.
62. Walker J, Hansen C, Butcher I, et al. Thoughts of death and suicide reported by cancer patients who endorsed the "suicidal thoughts" item of the PHQ-9 during routine screening for depression. Psychosomatics. 2011; 52: 424-427.
63. Yawn B, Pace W, Wollan P, et al. Concordance of Edinburgh Postnatal Depression Scale (EPDS) and Patient Health Questionnaire (PHQ-9) to assess increased risk of depression among postpartum women. J Am Board Fam Med. 2009; 22: 483-491.
64. Ballard ED, Ionescu DF, VandeVoort JL, et al. Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety. J Psychiatr Res. 2014; 58: 161-166.
65. Valuck R, Anderson HO, Libby AM, et al. Enhancing electronic health record measurement of depression severity and suicide ideation: a Distributed Ambulatory Research in Therapeutics Network (DARTNet) study. J Am Board Fam Med. 2012; 25: 582-593.
66. Wittkampf K, Naeije L, Schene A, et al. Diagnostic accuracy of the mood module of the Patient Health Questionnaire: a systematic review. Gen Hosp Psychiatry 2007; 29: 388-395.
67. Gilbody S, Richards D, Brealey S, et al. Screening for depression in medical settings with the Patient Health Questionnaire (PHQ): a diagnostic metaanalysis. J Gen Intern Med. 2007; 22: 1596-1602.
68. Razykov I, Hudson M, Baron M, et al. Canadian Scleroderma Research Group. Utility of the Patient Health Questionnaire-9 to assess suicide risk in patients with systemic sclerosis. Arthritis Care Res. 2013; 65: 753-758.
69. Razykov I, Ziegelstein RC, Whooley MA, et al. The PHQ-9 versus the PHQ-8—is item 9 useful for assessing suicide risk in coronary artery disease patients? Data from the Heart and Soul Study J Psychosom Res. 2012; 73: 163-168.
70. Johns SA, Kroenke K, Theobald DE, et al. Telecare management of pain and depression in patients with cancer: patient satisfaction and predictors of use. J Ambul Care Manage. 2011; 34: 126-139.
71. Desseilles M, Perroud N, Guillaume S, et al. Is it valid to measure suicidal ideation by depression rating scales? J Affect Disord. 2012: 136: 398-404.
72. Na PJ, Yaramala SR, Kim JA, et al. The PHQ-9 Item 9 based screening for suicide risk: a validation study of the Patient Health Questionnaire (PHQ)-9 Item 9 with the Columbia Suicide Severity Rating Scale (C-SSRS). J Affect Disord. 2018; 232: 34-40.
73. Beck AT, Kovacs, Weissman A. Assessment of suicidal intention: the scale for suicide ideation. J Consult Clin Psychol. 1979; 47: 343-352.
74. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide severity rating scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011; 168: 1266-1277.
75. Jobes DA, Nelson KN, Peterson EM, et al. Describing suicidality: an investigation of qualitative SSF responses. Suicide Life Threat Behav. 2004; 34: 99-112.
76. Trivedi MH, Wisniewski SR, Morris DW, et al. Concise Health Risk Tracking scale: a brief self-report and clinician rating of suicidal risk. J Clin Psychiatry. 2011; 72: 757-764.
77. Jhang JF, Hsu YH, Kuo HC. Possible pathophysiology of ketamine-related cystitis and associated treatment strategies. Int J Urol. 2015; 22: 816-825.