Understanding Suicide as a Public Health Issue

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Matthew Macaluso, D.O. has conducted clinical trials research as principal investigator for the following pharmaceutical companies over the last twelve months:

Acadia, Allergan, Alkermes, AssureRx/Myriad, Boehringer-Ingeleheim, Eisai, Lundbeck, Liva Nova, Janssen, Neurim, Otsuka, SAGE pharmaceuticals, Suven

All clinical trial and study contracts were with and payments made to the either the University of Alabama at Birmingham Medical Center or the Kansas University Medical Center Research Institute.

From April 2019 to June of 2020, Dr Macaluso was a member of the speaker bureau for Janssen pharmaceuticals (Spravato/esketamine).

Dr Macaluso has also received royalties from Springer Nature for his work as co-editor of the textbook titled Antidepressants: From Biogenic Amines to New Mechanisms of Action. This book was published in May of 2019.

Terminology

- From the Latin “self murder”
- Self inflicted death
- Suicide attempt—self injurious behavior with nonfatal outcome
- Para-suicidal behavior—self mutilation
- Aborted suicide attempt

Suicide

- Suicidal ideation—thoughts of wanting to die
- Suicidal intent—subjective expectation and desire to end one's life
- Suicidal plan

Incidence and Prevalence

- 250,000 suicide attempts annually in the United States
- 35,000 persons commit suicide annually in the United States
- Suicide rate 14.5 per 100,000 in US (2017)
- Scandinavia: highest rate in the world (25/100,000)
- Spain/Italy: lowest rate in the world

Alabama Data

- Suicide is the 11th leading cause of death in Alabama
- 834 Alabamians died by suicide in 2017
- 17.1 suicides per 100,000 population in Alabama
- Alabama has higher suicide rates than the national average since 1990

https://cdn4.creativecircleмedia.com/mountaineagle/files/20201003-092311-phpAIUaN9.pdf

Suicides in Alabama (2016)

County	Suicide Rate per 100,000
Elmore	44.3
Morgan	26.9
Calhoun	26.5
Lauderdale	25.7
Madison	25.3
Baldwin	23.5
Mobile	23.1
Shelby	23.0
Montgomery	21.8
Jefferson	21.7
Tuscaloosa	21.3
Cullman	20.1
Etowah	19.5
Marshall	19.1
Lee	18.2
St. Clair	17.9
Walker	16.9
Chambers	16.6
Jackson	14.7
Autauga	14.1
Blount	13.3
Coffee	12.7
DeKalb	12.5
Talladega	11.6
Escambia	10.8
Houston	10.7
Limestone	9.6

National rate: 13.5 per 100,000

20 of 27 counties exceed the national rate*

**with available data*

2009 VA Data

Males: 38.3 suicides per 100,000 population

Females: 12.8 suicides per 100,000 population

Military sexual trauma (MST) increases the risk

Greatest risk among those wounded multiple times or hospitalized for wounds

https://www.ptsd.va.gov/professional/co-occurring/ptsd-suicide.asp

Most Common Methods (nationally)

- Firearms (51.6%)
- Suffocation/hanging (22.6%)
- Poisoning (17.9%)

Trends in the Data

- Men commit suicide 3X more than women
- Women attempt suicide 4X more than men
- Men use more lethal methods (i.e. hanging)
- Rates increase with age
- Medical illness is a strong risk factor
- Most rapid rise among adolescents

Other Associated Risk Factors

- Race—risk lower in nonwhites, higher in Native Americans
- Religion—lowest in Catholics, Muslims, Jews
- Having young children is protective for women
- Marital status
  - Rate twice as high among singles
  - 4-5X increase risk among widowed, separated/divorced

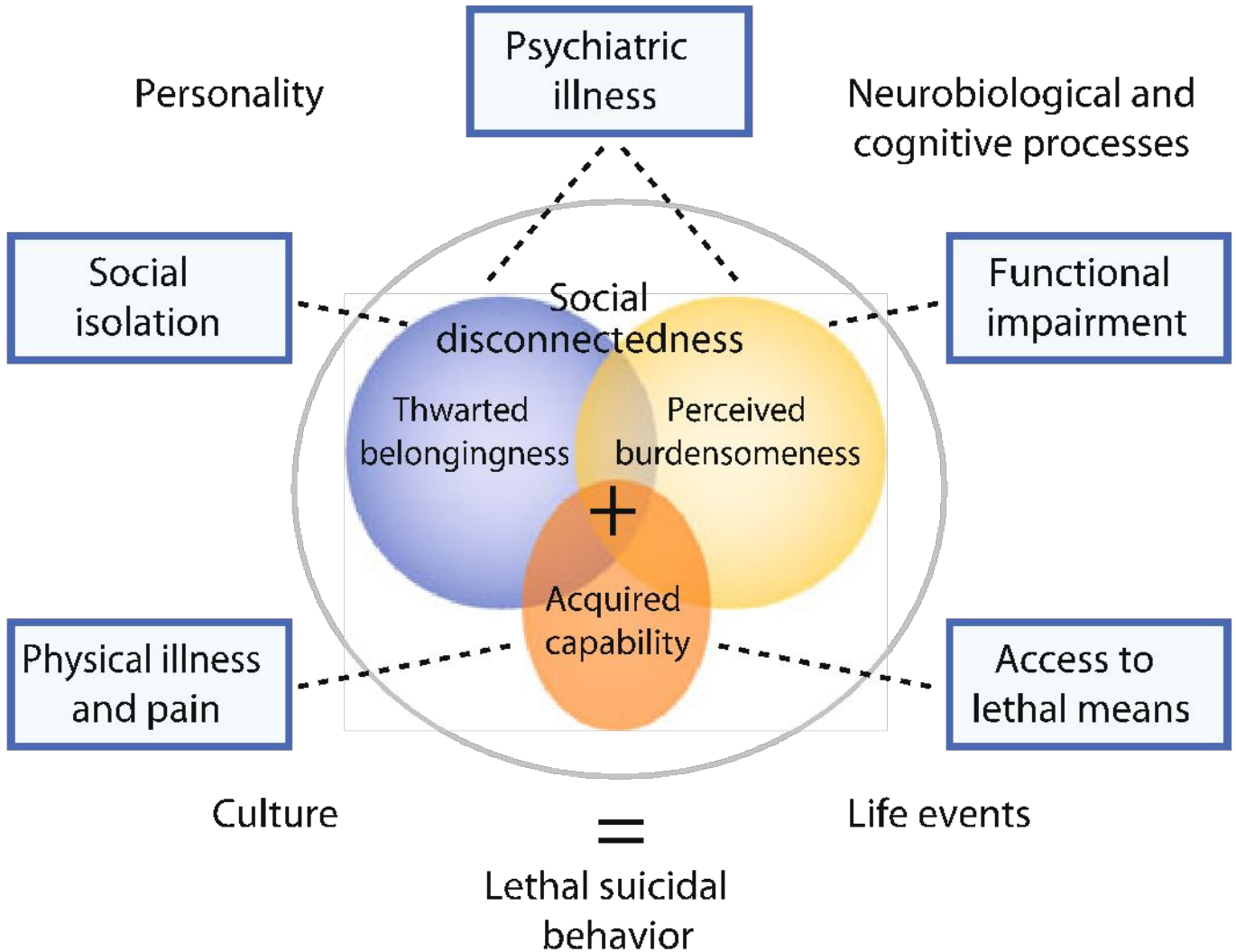
Older Adults

- Older adults make up 12% of the population
- Older adults account for 18% of deaths by suicide
- Older adults attempt less, but complete more often
- 65 and over: 15 suicides/100,000
- 75 and over: 17 suicides/100,000

American Association for Marital and Family Therapy

Older Adults

- Suicide among older adults may be underreported by as much as 40%
- High rates of completed suicide due to use of more lethal methods: firearms, hanging, drowning
- Death by suicide often mislabeled in older adults
- Doubles suicides (spouse and partner) occurs most commonly among elderly



Current Psychiatry Reports. June 2011, Vol 13, Issue 3, pp. 234-241

Anxiety Disorders

- Attempts made by 20% of patients with panic disorder and social phobia
- 1% of patients who commit suicide had a diagnosis of panic disorder
- Concomitant depression increases risks
- Some studies show preexisting anxiety as an independent risk factor

Mood Disorders

- 50% of all persons who commit suicide are depressed
- 15% of depressed patients commit suicide
- Patients with mood disorders accompanied by panic attacks are at highest risk
- Bipolar disorder—mixed features highest risk

Neurocognitive Disorders

- Haw and colleagues concluded that more research is needed to understand the relationship between neurocognitive disorders and suicide
- Most literature suggests a link between receiving a dementia diagnosis and suicide
- Rates vary by type of dementia (major neurocognitive disorder)

Haw C, Harwood D, Hawton K. Dementia and suicidal behavior: a review of the literature. Int Psychogeriatr. 2009;21:440–53.

Schizophrenia

- Early in course of illness
- 4,000 complete suicide per year in US
- 10% of persons who commit suicide have schizophrenia
- Prominent delusions are high risk
- Command hallucinations are high risk

Suicide risk in older adults with schizophrenia

Aging health. Author manuscript; available in PMC 2012 Apr 1.
Published in final edited form as:
Aging health. 2011 Jun; 7(3): 379–393.
doi: 10.2217/ahe.11.23

PMCID: PMC3198783
NIHMSID: NIHMS316977

Suicidal behavior in the older patient with schizophrenia

John Kasckow,[1,2,†] Lori Montross,[3] Laurie Prunty,[1] Lauren Fox,[1] and Sidney Zisook[4]

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Abstract

Go to:

Little is known about treating elderly suicidal patients with schizophrenia. The purpose of this article is to review the literature dealing with this population and to discuss what is required to advance this field. Most available studies from middle-aged and older individuals suggest that risk factors include hopelessness, lower quality of life, past traumatic events, depressive symptoms, lifetime suicidal ideation and past attempts; it is not clear whether these findings are generalizable to geriatric populations. Although little treatment research has been performed in older suicidal patients with schizophrenia, an integrated psychosocial and pharmacologic approach is recommended. In addition, one recent study augmented antipsychotic treatment with an SSRI (i.e., citalopram) in a sample of middle-aged and older individuals with schizophrenia with subsyndromal depression; in that study, serotonin selective reuptake inhibitor

Substance Use Disorders

- Suicide rate 20X higher for heroin dependent patients
- Alcohol dependence increases risk of suicide
- 2/3 of alcohol dependant patients who complete suicide also had mood disorders

Do Substance Use Disorders Increase Suicide Risk?

- People with substance use disorders are at **four to seven** times greater risk for death by suicide (Conner et al., 2019; San Too et al., 2019).

- SUDs may contribute more risk among women in veteran populations (Bohnert et al., 2016), but not the general population (Conner et al., 2019).

- However, other mental disorders and risk factors may explain the increased risk (Bohnert et al., 2016).
  - These numbers decrease when we account for other psychiatric disorders and other risk factors (e.g., job loss)

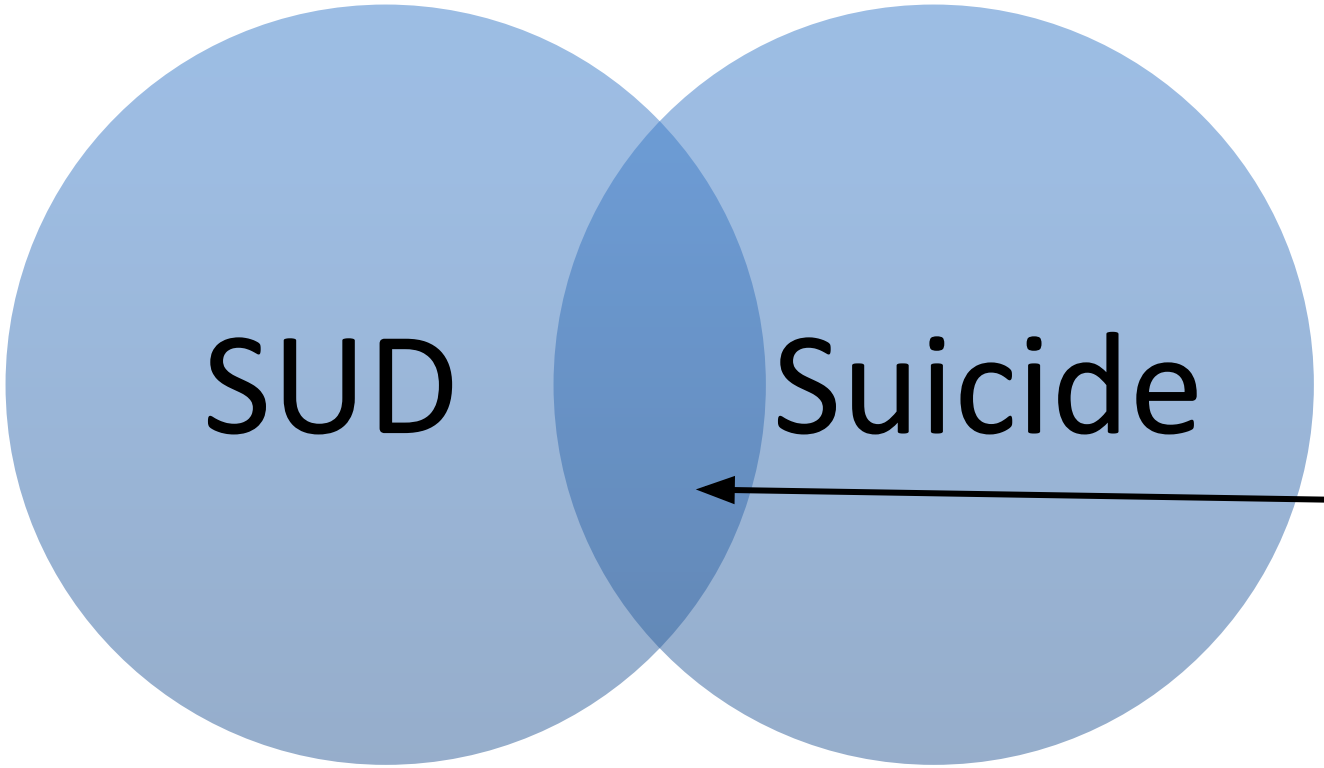
Which SUDs Contribute Most Risk?

Data are limited; less data on stimulant and cannabis

- **Alcohol use disorder:** 3 times risk (Darvishi et al., 2015)
- **Sedative use disorder**: 4-12 times risk (Bohnert et al., 2016)
- **Opioid use disorder**: 2-8 times risk (Bohnert et al., 2016)

Possible Explanations

- If we understand the *why,* may be able to target our prevention efforts.



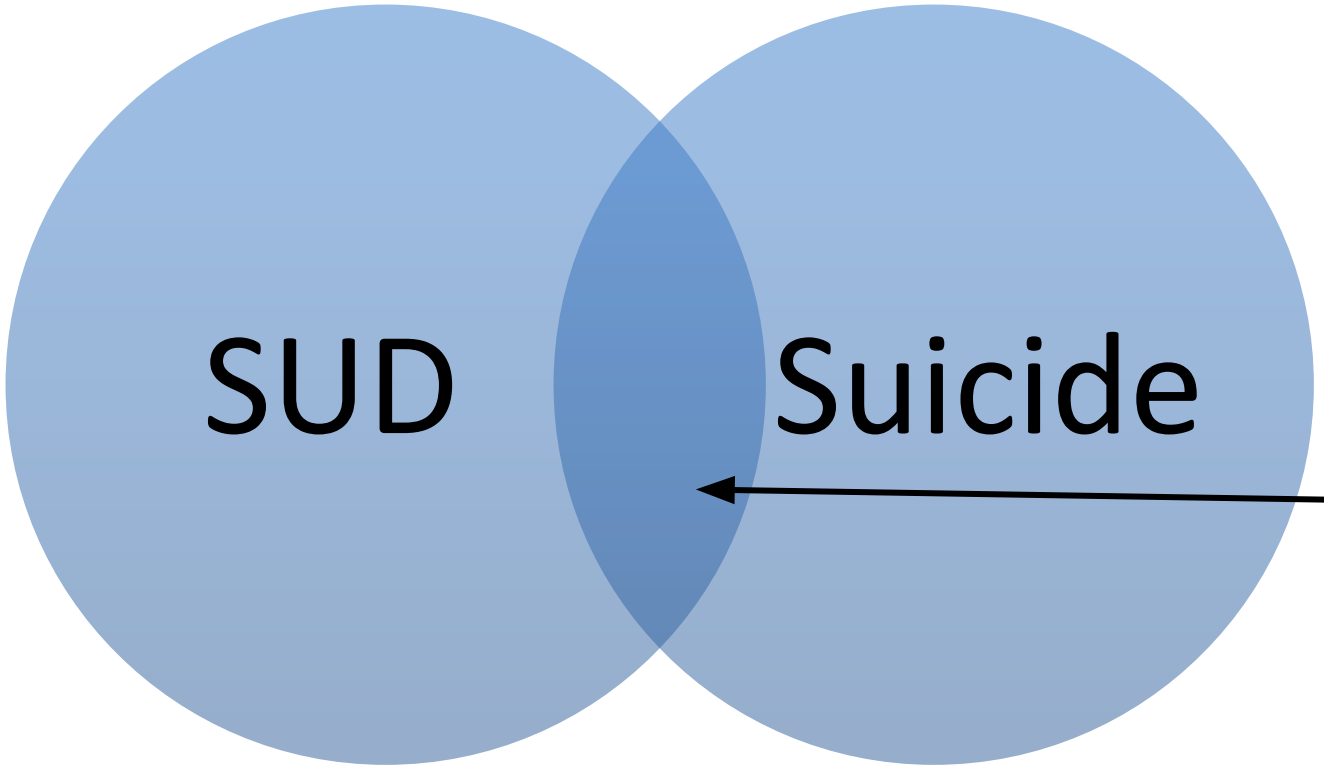
Shared Psychological and Social Factors

- Relationship dysfunction
- Occupational and financial stressors
- Comorbid psychiatric illnesses (depression, bipolar disorder, borderline personality disorder)
- History of childhood sexual abuse

Bohnert et al., 2016; Yuodelis-Flores et al., 2015

Possible Explanations

- If we understand the *why,* may be able to target our prevention efforts.



Shared Biological Factors

- Serotonin deficits (but see Underwood et al. 2018)
- Impaired activity in brain regions that involve self-control, planning, inhibition

Costanza et al., 2020; Serafini et al., 2016

Example: Suicide in the context of opioid transitions

VA patients whose opioid treatment for pain was stopped were at greater risk for death, including suicide (Oliva et al., 2020)

Example: Alcohol Withdrawal

- Alcohol withdrawal impact on suicide

Letter to the Editor

IJSP

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DOI: 10.1177/0020764020938809
journals.sagepub.com/home/isp
SAGE

COVID-19 lockdown in India triggers a rapid rise in suicides due to the alcohol withdrawal symptoms: Evidence from media reports

Shakil Ahmed[1], M Omar Khaium[2] and Fabeha Tazmeem[1]

Example: Acute Alcohol Intoxication

- 34% of suicide decedents have a nonzero level of alcohol in their blood at time of death (Anestis et al., 2015).
- Some theorists believe that alcohol intoxication can amplify existing mood (tears in the beer effect) and increase risk (e.g., Hufford, 2001).
- Additionally, people may become more aggressive, fearless, or impulsive as a result of drinking, enabling them to attempt suicide (Wolford-Clevenger et al., 2015; 2018).

PTSD and Suicide

- Higher levels of intrusive memories can predict relative risk for suicide
- Some studies show a link between suicide, PTSD and either antisocial personality or depression
- When controlled for co-morbidities, PTSD appears to increase the risk for suicide

https://www.ptsd.va.gov/professional/co-occurring/ptsd-suicide.asp

Personality Disorders

- Patients with PD have 7X increased risk
- BPD associated with parasuicidal behaviors
- BPD patients with high impulsivity at increased risk
- Incarcerated APD patients with high risk
- Prisoners have highest suicide rate of any group

Interview Techniques

- Conflicting data on rating scales
- Some evidence supports semi-structured interviewing
- "Identify modifiable, treatable risk and protective factors"—APA treatment guidelines
- The US Preventive Task Force does not recommend universal screening in primary care
- Therapeutic alliance a protective factor

Intervention Trials

- Increased connectedness decreased suicide in older adults in two studies
- Both studies were more than 10 years long and used telephone-based outreach and support
- Japanese studies used health education, volunteer and peer support activities

De Leo D, Dello Buono M, Dwyer J. Suicide among the elderly: the long-term impact of a telephone support and assessment intervention in northern Italy. Br J Psychiatry. 2002;181:226–9.

Oyama H, Sakashita T, Ono Y, Goto M, Fujita M, Koida J. Effect of community-based intervention using depression screening on elderly suicide risk: a meta-analysis of the evidence from Japan. Community Ment Health J. 2008;44:311–20.

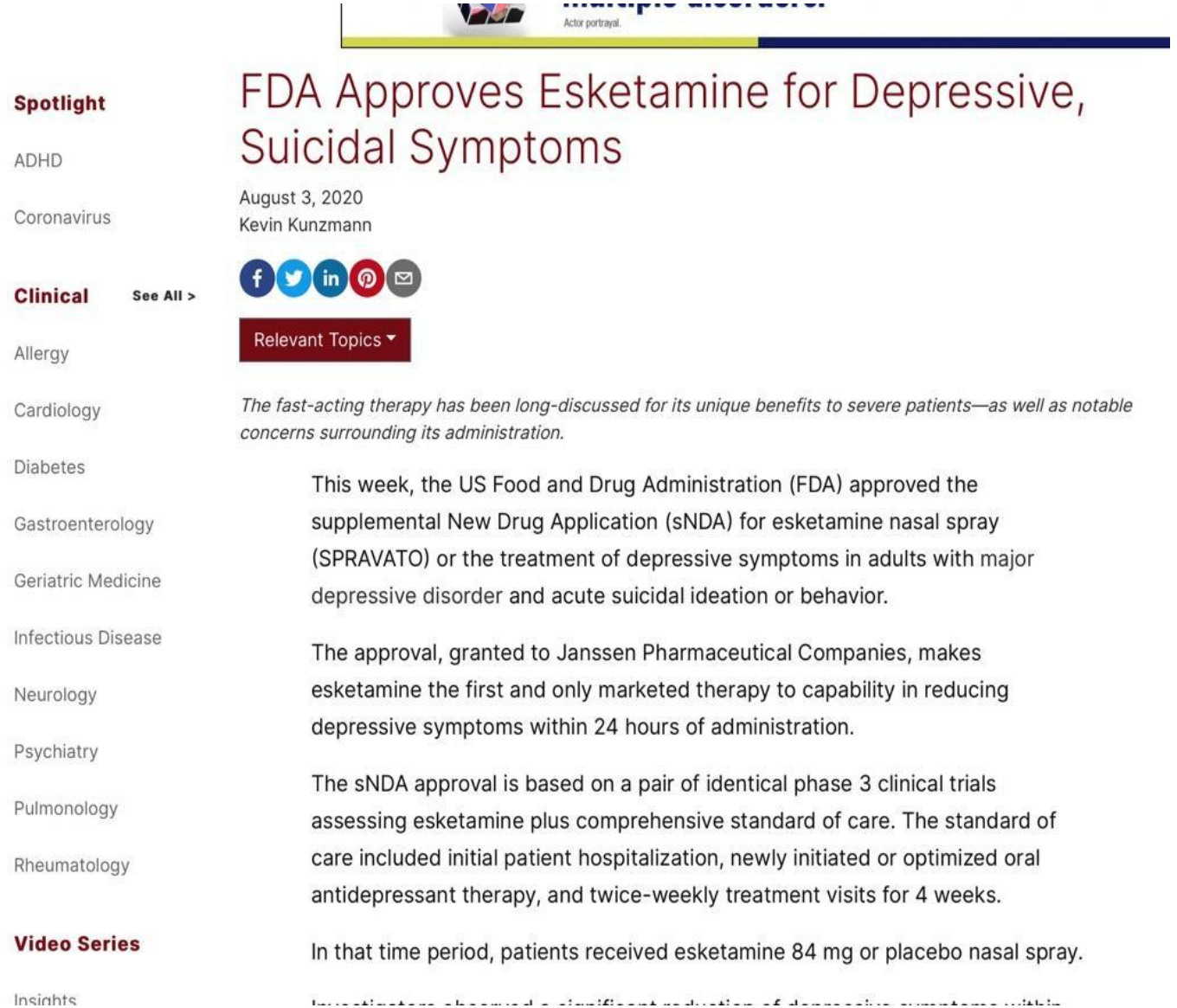
PROSPECT Trials

- Intervention used a collaborative care model of care managers, algorithm guided medication management, and interpersonal therapy
- Results showed decrease in suicidal ideation over a two year period
- The collaborative model improved social connectedness

Alexopoulos GS, Reynolds CF, III, Bruce ML, et al. Reducing suicidal ideation and depression in older primary care patients: 24-month outcomes of the PROSPECT study. Am J Psychiatry 2009. doi:10.1176/appi.ajp.2009.08121779. This article describes 2- year outcomes of a collaborative care model designed to reduce suicidal ideation among older adults and represents one of the largest and most well-designed clinical trials for the prevention of late-life suicidality.

Psychopharmacology

- Lithium
  - Decreases suicide risk in bipolar patients
- Clozapine
  - Decreases suicide risk in schizophrenic and schizoaffective patients
- Esketamine
  - FDA indication for suicidality



Spotlight

ADHD

Coronavirus

Clinical See All >

Allergy

Cardiology

Diabetes

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Geriatric Medicine

Infectious Disease

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Psychiatry

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Insights

FDA Approves Esketamine for Depressive, Suicidal Symptoms

August 3, 2020
Kevin Kunzmann

Relevant Topics

The fast-acting therapy has been long-discussed for its unique benefits to severe patients—as well as notable concerns surrounding its administration.

This week, the US Food and Drug Administration (FDA) approved the supplemental New Drug Application (sNDA) for esketamine nasal spray (SPRAVATO) or the treatment of depressive symptoms in adults with major depressive disorder and acute suicidal ideation or behavior.

The approval, granted to Janssen Pharmaceutical Companies, makes esketamine the first and only marketed therapy to capability in reducing depressive symptoms within 24 hours of administration.

The sNDA approval is based on a pair of identical phase 3 clinical trials assessing esketamine plus comprehensive standard of care. The standard of care included initial patient hospitalization, newly initiated or optimized oral antidepressant therapy, and twice-weekly treatment visits for 4 weeks.

In that time period, patients received esketamine 84 mg or placebo nasal spray.

https://www.hcplive.com/view/fda-approves-esketamine-depressive-suicidal-symptoms

509

Rapid Reduction of Major Depressive Disorder Symptoms in Adult Patients at Imminent Risk for Suicide: ASPIRE II, a Phase 3 Randomized Study of Esketamine Nasal Spray

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Janssen Research & Development, LLC, Titusville, NJ
*Presenting Author

BACKGROUND

- Major depressive disorder (MDD) is the mental health condition most commonly associated with suicide.[1]
- Patients with MDD presenting with active suicidal ideation (SI) with intent constitute a psychiatric emergency that requires immediate intervention. Additionally, these patients are typically excluded from clinical trials of antidepressants.
- Current conventional antidepressants are of limited use due to delayed (4 to 6 weeks) onset of action.[2]
- In a phase 2 proof-of-concept study, esketamine nasal spray (ESK) in addition to comprehensive standard-of-care (SOC) demonstrated rapid reduction in depressive symptoms at 4 hours after an initial dose in patients with MDD at imminent risk for suicide.[3]
- Efficacy and safety of ESK was further evaluated in ASPIRE II, one of two phase 3 studies in the first global registration program in an understudied population of patients with MDD at imminent risk for suicide.

OBJECTIVES

Primary objective

- To evaluate the efficacy of ESK+SOC vs placebo+SOC in rapidly reducing the symptoms of MDD, including SI, in patients at imminent risk for suicide.

Key secondary objective

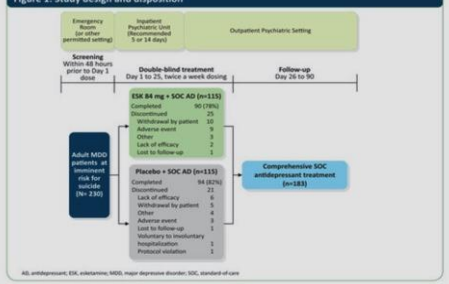
- To assess the efficacy of ESK+SOC vs placebo+SOC in rapidly reducing the severity of suicidality in patients with MDD at imminent risk for suicide.

METHODS

Study overview

- ASPIRE II (NCT03097133) is a double-blind (DB), randomized, placebo-controlled phase 3 study conducted in Argentina, Austria, Belgium, Brazil, Canada, Czech Republic, France, Lithuania, Poland, Spain, Turkey and the United States.
- Patients were randomized (1:1) to either ESK (84 mg) or placebo twice-weekly for 4 weeks (DB phase) in addition to comprehensive SOC (includes initial inpatient hospitalization and newly initiated or optimized antidepressant therapy, enhanced by twice-weekly intensive visits during the DB phase).
- Results from the DB phase are reported in this poster.

Figure 1: Study design and disposition



Eligibility criteria

Inclusion criteria
• Men or women aged 18 to 64 years
• DSM-5 diagnosis of MDD, without psychotic features
• Current SI with intent, within 24 hours of randomization, confirmed by a "Yes' to the questions "Think about suicide [killing yourself]?" and "Intend to act on thoughts of killing yourself?"
• In need of acute psychiatric hospitalization due to imminent risk of suicide and admitted voluntarily
• MADRS total score of >28 predose on Day 1
Exclusion criteria
• Current DSM-5 diagnosis of bipolar (or related disorders), obsessive compulsive disorder, antisocial personality disorder, or borderline personality disorder
• Current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychosis
• DSM-5 diagnosis of moderate or severe substance or alcohol use disorder within 6 months before screening*
• SBP >140 mm Hg or DBP >90 mm Hg
• Positive urine test result(s) for phencyclidine, cocaine, or amphetamines

*12 months before screening for certain EU countries; DBP, diastolic blood pressure; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, fifth edition; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; SBP, systolic blood pressure

- Suicide Ideation and Behavior Assessment Tool (SIBAT) is a computerized tool containing patient-reported modules and clinician assessments to evaluate efficacy and safety based changes in SIB.

Study assessments

- ***Primary efficacy endpoint:*** Change from baseline (Day 1, predose) to 24 hours after first dose in depressive symptoms, as measured by Montgomery–Åsberg Depression Rating Scale (MADRS) total score
- ***Key secondary endpoint:*** Change from baseline (Day 1, predose) to 24 hours after first dose in severity of suicidality, as measured by Clinical Global Impression-Severity of Suicidality-Revised (CGI-SS-R) from the SIBAT
- ***Other efficacy endpoints:*** Following were measured at 4 hours and 24 hours after first dose and through the end of DB treatment phase (Day 25)
  - Remission of MDD (MADRS total score ≤12)
  - Reduction in Clinical Global Impression of Imminent Suicide Risk (CGI-SR-I) and changes in Frequency of Suicidal Thinking (FoST), clinician-rated and patient-reported outcomes from the SIBAT.
  - MADRS suicidal thoughts item (Item 10)
- ***Safety:*** Treatment-emergent adverse events (TEAEs) were monitored.

Statistical methods

- ***Sample size calculation***

Sample was calculated assuming an effect size of 0.45 for the change in MADRS total score between ESK and placebo, a two-sided significance level of 0.05, and a drop-out rate of 5% at 24 hours. Approximately 112 patients were planned to be randomized to each treatment group to achieve 90% power.

- ***Statistical hypothesis testing***

Statistical analysis tests were conducted at a two-sided 0.05 significance level. The testing of multiple endpoints (primary and key secondary), was controlled by a fixed sequence testing procedure, i.e., the key secondary hypothesis will be tested only after the null hypothesis for the primary endpoint is rejected.

- Primary efficacy endpoint was analyzed based on last observation carried forward (LOCF) using an analysis of covariance (ANCOVA) model with factors for treatment (placebo or ESK), analysis center and SOC antidepressant treatment as randomized and baseline value as a covariate. Treatment effects were estimated using least squares (LS) means. In addition, the treatment effect was estimated using a mixed-effects model using repeated measures (MMRM) based on observed case data.
- Key secondary efficacy endpoint was analyzed based on LOCF data using an ANCOVA model on the ranks of change with factors for treatment, analysis center and SOC antidepressant treatment as randomized and baseline unranked score as a covariate. The treatment effect was estimated using the Hodges-Lehmann estimate and an item response theory (IRT) model.
- Other efficacy endpoints and safety were also summarized descriptively.

Analyses sets

- ***Full efficacy analysis set***: All randomized patients who received ≥1 dose of study medication and have both a baseline and a post dose evaluation for the MADRS total score or CGI-SS-R.
- ***Safety analysis set***: All randomized patients who received ≥1 dose of study medication.

RESULTS

- Study was conducted from 22 June 2017 to 11 April 2019.
- 230 patients were randomized to treatments: ESK+SOC, n=115; placebo+SOC, n=115
- 184 of 230 (80.0%) patients completed the DB treatment phase.
- Baseline characteristics were comparable between the treatment groups.

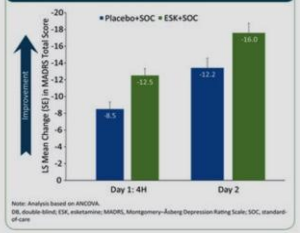
Table 1: Demographics and baseline characteristics (Full efficacy analysis set)

	Placebo+SOC (n=113)	ESK (84 mg) +SOC (n=114)
Age, years, mean (SD)	41.4 (13.43)	40.2 (12.73)
Sex, n (%)		
Women	67 (59.3)	69 (60.5)
MADRS total score, mean (SD)	39.9 (5.76)	39.5 (5.19)
CGI-SS-R, n (%)		
Questionably suicidal	3 (2.7)	1 (0.9)
Mildly suicidal	6 (5.3)	10 (8.8)
Moderately suicidal	33 (29.2)	35 (30.7)
Markedly suicidal	42 (37.2)	48 (42.1)
Severely suicidal	28 (24.8)	17 (14.9)
Extremely suicidal	1 (0.9)	3 (2.6)
Prior suicide attempt	72 (63.7)	78 (68.4)
Suicide attempt within the last month	24 (21.2)	36 (31.6)
SOC antidepressants as randomized		
Antidepressants monotherapy	43 (38.1)	45 (39.5)
Antidepressants + augmentation therapy	70 (61.9)	69 (60.5)

CGI-SS-R, Clinical Global Impression – Severity of Suicidality – Revised; ESK, esketamine; MADRS, Montgomery–Åsberg Depression Rating Scale; SD, standard deviation; SOC, standard-of-care

Efficacy

Figure 2: LS Mean change in MADRS total score from baseline at day 1 (4 hours postdose) and day 2 (~24 hours postdose) (DB treatment phase; Full efficacy analysis set)



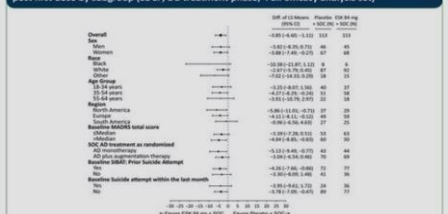
Note: Analysis based on ANCOVA.
DB, double-blind; ESK, esketamine; MADRS, Montgomery–Åsberg Depression Rating Scale; SOC, standard-of-care

Primary endpoint

- Treatment with ESK+SOC showed statistically significant improvement (reduction from baseline in MADRS total scores) in depressive symptoms vs placebo+SOC (LS mean [SE] difference: −3.9 [1.39]; p=0.006) at 24 hours post first dose.

- In most subgroups, the treatment differences were consistent with the primary analysis.

Figure 3: LS mean treatment difference of change from baseline MADRS total score to 24 hours post first dose by subgroup (LOCF; DB treatment phase; Full efficacy analysis set)

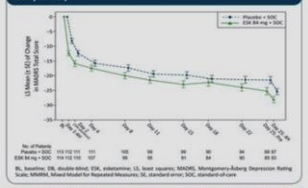


AD, antidepressant; DB, double-blind; ESK, esketamine; LS, least squares; LOCF, last observation carried forward; MADRS, Montgomery-Åsberg Depression Rating Scale; SIBAT, Suicide Ideation and Behavior Assessment Tool; SOC, standard-of-care

Key secondary endpoint

- Both treatments showed improvements in severity of suicidality scores at 24 hours after first dose (change from baseline in CGI-SS-R scores, median [range]: ESK+SOC, −1.0 [−6; 2]; placebo+SOC, −1.0 [−5; 2]); however, the treatment difference was not significant (p=0.379).

Figure 4: LS mean changes in MADRS total score over time during the DB treatment phase (MMRM; Observed case; Full efficacy analysis set)



BL, baseline; DB, double-blind; ESK, esketamine; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, Mixed Model for Repeated Measures; SE, standard error; SOC, standard-of-care

Other secondary endpoints

- For depressive symptoms, the treatment difference numerically favored ESK+SOC starting at 4 hours after initial dose and at all timepoints during the DB treatment phase.

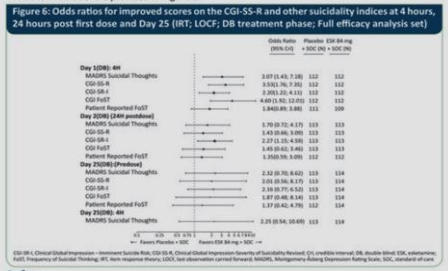
Figure 5: MADRS remission rates over time during the DB treatment phase (Full efficacy analysis set)

DB, double-blind; ESK, esketamine; MADRS, Montgomery-Åsberg Depression Rating Scale; SE, standard error; SOC, standard-of-care

- More patients in ESK+SOC vs placebo+SOC achieved remission at 4 hours and 24 hours after first dose and Day 25.

- Findings of all indices of suicidality (CGI-SS-R, the MADRS suicidal thoughts item, CGI-SR-I, clinician-rated FoST, and patient-reported FoST) at 4 hours and 24 hours post first dose and Day 25, based on the IRT model are provided in Figure 6.

Figure 6: Odds ratios for improved scores on the CGI-SS-R and other suicidality indices at 4 hours, 24 hours post first dose and Day 25 (IRT; LOCF; DB treatment phase; Full efficacy analysis set)



CGI-SR-I, Clinical Global Impression – Imminent Suicide Risk; CGI-SS-R, Clinical Global Impression-Severity of Suicidality-Revised; CrI, credible interval; DB, double-blind; ESK, esketamine; FoST, Frequency of Suicidal Thinking; IRT, item response theory; LOCF, last observation carried forward; MADRS, Montgomery-Åsberg Depression Rating Scale; SOC, standard-of-care

Safety

- Overall, 104 (91.2%) patients in the ESK+SOC group and 87 (77.0%) in the placebo+SOC group experienced ≥1 TEAE during the DB phase.
- The most common TEAEs (>10% of patients) in ESK+SOC vs placebo+SOC group were dizziness (41% vs 19%), dissociation (39% vs 8%), nausea (33% vs 14%), dysgeusia (25% vs 16%), somnolence (23% vs 11%), headache (22% vs 23%), paraesthesia (20% vs 6%), vomiting (16% vs 4%), anxiety (15% vs 6%), vision blurred (15% vs 5%), sedation (14% vs 3%), paraesthesia oral (12% vs 3%), euphoric mood (11% vs 1%) and hypoesthesia (11% vs 1%).
- Serious TEAEs were reported in 11 patients in the DB phase.
  - ESK+SOC: suicide attempt (n=3), suicidal ideation and depersonalization/derealization disorder (n=1 each)
  - Placebo+SOC: suicide attempt (n=3), suicidal ideation (n=2), depression, arrhythmia, pericardial effusion and pneumothorax (n=1 each)
- No deaths were reported in either the DB or follow-up phase.

DISCUSSION & CONCLUSIONS

- This is the first global registration program of patients with active SI and intent, a vulnerable and heretofore understudied population for whom there is great unmet medical need.
- At 24 hours after the first dose of study medication (primary endpoint), ESK plus comprehensive SOC demonstrated a clinically meaningful and statistically significant reduction of depressive symptoms.
- For depressive symptoms, the treatment difference numerically favored ESK+SOC starting at 4 hours after the initial dose and at all timepoints during the DB treatment phase.
- Although both treatment groups experienced improvement in severity of suicidality from baseline to 24 hours after first dose, the difference between treatment groups was not statistically significant.
  - This may be due to the substantial beneficial effects of inpatient psychiatric hospitalization in diffusing the acute suicidal crisis in patients in both treatment groups.
- Safety findings were consistent with the known profile of ESK.

References:
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Thank you!

References available upon request