



Co-Occurring Mental Disorders and Risk of Suicide in a National Cohort of Male Veterans

Kenneth R. Conner, Amy S. Bohnert, John F. McCarthy,
Marcia Valenstein, Robert Bossarte, Rosalinda Ignacio,
Naiji Lu, & Mark A. Ilgen

VA VISN 2 Center of Excellence for Suicide Prevention,
University of Rochester Medical Center Departments of Psychiatry and Biostatistics,
VA Serious Mental Illness Treatment Resource and Evaluation Center,
University of Michigan Department of Psychiatry

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Suicide in Veterans Treated in VHA

Veterans Health Administration (VHA) is largest integrated health care system in U.S.

Annually more than 1,600 VHA users die by suicide (McCarthy et al., 2009)

Veterans who use VHA services are at increased risk for suicide (McCarthy et al., 2009)





Psychiatric Comorbidity and Suicide

Comorbidity = 2-plus mental disorders

Most data on comorbidity from psychological autopsy studies
(Cavanagh et al., 2003; Yoshimasu et al., 2008)

Comorbidity commonly present in suicide, with depression +
substance use disorder (SUD) most common (Cavanagh et al.,
2003; Yoshimasu et al., 2008)

Comorbidity more common among suicides compared to non-suicide
controls (Hawton et al., 2002; Kim et al., 2003; Lesage et al., 1994;
Waern et al., 2002)





Synergism Hypothesis

Synergism = more than additive

Psychiatric comorbidity in suicide has led to hypotheses of synergism (Cheng et al., 1995; Conner et al., 2003; Yoshimasu et al., 2008)

Formal tests of synergism using psychological autopsy data have not supported the hypothesis (Cheng et al., 2000; Conner et al., 2003; Zhang et al., 2012)

Lack of evidence may indicate that risk conferred by psychiatric disorders in combination is not synergistic, or may be due to low statistical power





Purpose of Study

To examine comorbidity in Veterans using VHA services

We hypothesized that risk conferred by 2-way combinations of disorders is more than additive (i.e., synergistic)

We also examined numbers of mental disorders, regardless of type

Limited analyses to men (insufficient women in database to examine comorbidity)





Study Population

Previously described (Ilgen et al., 2010)

Cohort included all men who utilized VHA services in fiscal year (FY) 1999 and were alive at the start or FY 2000

N= 2,962,810

Cohort was followed until death or the end of FY 2006, whichever came first.





Data Sources

Linkage of two databases

- 1) Centers for Disease Control National Death Index (NDI)
- 2) VA National Patient Care Database (NPCD)

Suicide determinations from NDI

Mental disorder diagnoses based on ICD-9 codes in NPCD

Used 6 categories of diagnoses:

- 1) PTSD, 2) SUD, 3) depression, 4) bipolar disorder,
- 5) anxiety disorder except PTSD, 6) schizophrenia





Analyses

Calculations used cohort who used VHA services in FY 1999 and were alive at start of FY 2000

Time of observation began first day of FY 2000 and ended at date of death or last day of FY 2006

Covariance sandwich estimates were used to adjust for clustering of data within VHA facilities

All analyses adjusted for age

Sensitivity analyses of suicides in FY 2000





Analyses Cont'd

Used a series of proportional hazards regression models

Models yielded estimates of risk based on Hazard Ratios and 95% Confidence Intervals (HR, 95% CI)

Two sets of analyses:

- 1) Estimated risk for each diagnostic category, irrespective of comorbidity
- 2) Estimated risk associated with each 2-way combination (e.g., PTSD + SUD), irrespective of further comorbidity





Analyses Cont'd

To examine synergism, we conducted 15 two-way interaction tests

In these models we included 1) the main effect for a diagnosis irrespective of comorbidity (e.g., SUD), 2) the main effect for a second diagnosis irrespective of comorbidity (e.g., depression), and 3) the two-way interaction term

Statistically significant interaction tests were interpreted to indicate that the null hypothesis of additivity should be rejected.

Model fits assessed with Likelihood Ratio tests.

Alpha set to .05





Analyses Cont'd

We also described the number of suicide decedents with a total of 0, 1, 2, 3, 4, 5, and 6 (all possible) mental disorders.

Calculated risk for suicide associated with each number (e.g., one disorder, two disorders, etc.) in a multivariate model, using a no disorder reference group.





Descriptive Results

7,426 (0.25%) male suicides between FY 2000 and FY 2006.

3,456 (46.5%) suicides diagnosed with one or more mental disorders in FY 1999.

Depression was most common, followed by SUD

Most suicides with a diagnosis showed comorbidity

Each disorder or 2-way combination conferred significant risk for suicide.





Descriptive Data (Suicides, N=7426)

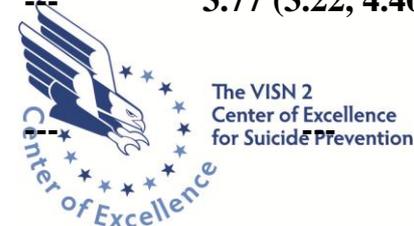
Diagnosis	Disorder Itself N (%)	Comorbid Substance N (%)	Comorbid Depression N (%)	Comorbid Bipolar N (%)	Comorbid Anxiety N (%)	Comorbid Schiz. N (%)
PTSD	869 (11.7%)	419 (5.6%)	618 (8.3%)	189 (2.5%)	320 (4.3%)	155 (2.1%)
SUD	1,583 (21.3%)	---	977 (13.2%)	330 (4.4%)	462 (6.2%)	281 (3.8%)
Dep.	2,281 (30.7%)	---	---	482 (6.5%)	792 (10.7%)	399 (5.4%)
Bipolar	638 (8.6%)	---	---	---	230 (3.1%)	229 (3.1%)
Anxiety	1,080 (14.5%)	---	---	---	---	186 (2.5%)
Schiz.	660 (8.9%)	---	---	---	---	---





Risk associated with Mental Disorders and Comorbidities

Diagnosis	Disorder Itself HR (95% CI)	Comorbid Substance HR (95% CI)	Comorbid Depression HR (95% CI)	Comorbid Bipolar HR (95% CI)	Comorbid Anxiety HR (95% CI)	Comorbid Schiz. HR (95% CI)
PTSD	2.60 (2.39, 2.82)	3.81 (3.40, 4.27)	3.07 (2.79, 3.37)	4.52 (3.87, 5.29)	3.26 (2.91, 3.65)	3.42 (2.88, 4.05)
SUD	2.98 (2.76, 3.21)	---	4.27 (3.89, 4.68)	5.19 (4.57, 5.90)	4.82 (4.31, 5.39)	3.68 (3.20, 4.24)
Dep.	3.01 (2.84, 3.19)	---	---	4.85 (4.37, 5.37)	3.48 (3.20, 3.78)	3.82 (3.38, 4.32)
Bipolar	4.29 (3.91, 4.71)	---	---	---	5.20 (4.46, 6.07)	4.35 (3.76, 5.04)
Anxiety	2.79 (2.57, 3.02)	---	---	---	---	3.77 (3.22, 4.40)
Schiz.	3.04 (2.77, 3.32)	---	---	---	---	---





Synergism Results

14 of 15 two-way interaction tests had a negative beta (β) and reached statistical significance (e.g., PTSD x SUD ($\beta = -0.246$, $p = .0003$)).

These results indicate that the null hypothesis that the relationship between disorders in suicide risk is additive should be rejected. However, the fact that the betas were universally negative is contrary to the hypothesis of synergism.

We interpret the results to indicate *subadditive risk* (i.e., greater risk or similar risk in two disorders compared to each considered separately along with a significant two-way interaction term with a negative beta)





Number of Disorders and Suicide Risk

# Mental Disorders	N (%)	HR (95% CI)
0	3,970 (53.5%)	1.00 (ref)
1	1,431 (19.3%)	1.99 (1.87, 2.12)
2	994 (13.4%)	2.69 (2.51, 2.89)
3	589 (7.9%)	3.27 (2.98, 3.59)
4	313 (4.2%)	4.46 (3.88, 5.14)
5	101 (1.4%)	4.74 (3.87, 5.82)
6	28 (0.4%)	6.70 (4.49, 10.00)





Number of Disorders and Suicide Risk

The number of suicide decedents decreased as the number of diagnoses increased.

Although the HRs increased as the number of diagnoses increased, nonetheless results appeared consistent with **subadditivity**, with risk not increasing as much as expected (e.g., 3 disorders) considering risk associated with fewer disorders (e.g., 1 and 2 disorders).

We performed post-hoc analyses to determine if there is a **linear trend** in the hazards ratios as the number diagnoses increases (as visual inspection of the table suggests). This post-hoc analysis was consistent with a linear trend.





Sensitivity Analysis FY 2000 Descriptive Results

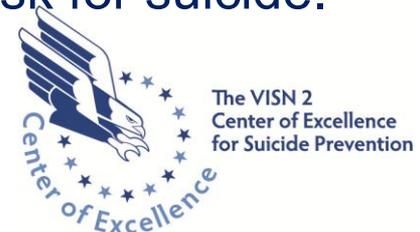
1,203 (0.04%) male suicides in FY 2000, representing 16.2% of suicides in the cohort.

633 (52.6%) suicides were diagnosed with one or more mental disorders in FY 1999.

Depression was most common, followed by SUD

Most suicides with a diagnosis showed comorbidity

Each disorder or 2-way combination conferred significant risk for suicide.





Sensitivity Analysis, FY 2000 Descriptive Data (Suicides, N=1203)

Diagnosis	Disorder Itself N (%)	Comorbid Substance N (%)	Comorbid Depression N (%)	Comorbid Bipolar N (%)	Comorbid Anxiety N (%)	Comorbid Schiz. N (%)
PTSD	160 (13.3%)	83 (6.9%)	111 (9.2%)	40 (3.3%)	57 (4.7%)	30 (2.5%)
SUD	310 (25.8%)	---	198 (16.5%)	75 (6.2%)	99 (8.2%)	61 (5.1%)
Dep.	420 (34.9%)	---	---	103 (8.6%)	165 (13.7%)	78 (6.5%)
Bipolar	133 (11.1%)	---	---	---	58 (4.8%)	54 (4.5%)
Anxiety	221 (18.4%)	---	---	---	---	39 (3.2%)
Schiz.	123 (10.2%)	---	---	---	---	---



Sensitivity Analysis, FY2000

(Risk assoc with Mental Disorders and Comorbidities)



Diagnosis	Disorder Itself HR (95% CI)	Comorbid Substance HR (95% CI)	Comorbid Depression HR (95% CI)	Comorbid Bipolar HR (95% CI)	Comorbid Anxiety HR (95% CI)	Comorbid Schiz. HR (95% CI)
PTSD	3.41 (2.84, 4.09)	5.43 (4.26, 6.91)	3.89 (3.18, 4.77)	6.91 (4.94, 9.66)	4.03 (3.15, 5.17)	4.75 (3.24, 6.70)
SUD	4.03 (3.46, 4.68)	---	6.08 (5.06, 7.30)	8.31 (6.42, 10.77)	7.22 (5.82, 8.97)	5.76 (4.33, 7.67)
Dep.	3.78 (3.31, 4.30)	---	---	7.23 (5.78, 9.05)	4.98 (4.22, 5.87)	5.23 (4.02, 6.80)
Bipolar	6.25 (5.08, 7.69)	---	---	---	9.21 (7.04, 12.04)	7.20 (5.30, 9.79)
Anxiety	3.91 (3.35, 4.55)	---	---	---	---	5.54 (4.00, 7.66)
Schiz.	3.93 (3.19, 4.84)	---	---	---	---	---



The VISN 2
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for Suicide Prevention



Sensitivity Analyses, FY 2000

Slightly higher percentage of suicides had mental disorder diagnosis
(52.6% vs. 46.5%)

Risk associated with mental disorders and two-way combinations was
universally higher than for the overall cohort

Same pattern of diagnoses, with depression and SUD most common

Similar results with tests of comorbidity, with 13 of 15 two-way
combinations showing subadditivity





Precedence for Subadditivity

A large Danish cohort showed an interaction between alcohol use disorder (AUD) and other mental disorders in suicide risk. Follow-up analysis showed AUD conferred higher risk in those without mental disorder than those with a disorder (Flensburg-Madsen et al., 2009).

In a very large case-control psychological autopsy study of males in China (N=969 suicides), a statistically significant interaction between AUD and major depression showed that risk conferred by major depression was weaker among men with AUD (Zhang et al., 2012).

Analysis of World Mental Health Survey showed that risk for a lifetime suicide attempt associated with each additional mental disorder was subadditive, with the degree of increased risk “decaying” with each additional disorder (Nock et al., 2009).





Limitations

- Mental disorder diagnoses were based on clinical records.
- Other comorbidities, including physical illnesses, were not analyzed.
- The study population was men treated in VHA, with unclear relevance to other populations.
- Because a small percentage of male VHA users are not Veterans, it was not strictly a Veteran sample.
- The diagnoses were made in advance of suicide and do not necessarily reflect symptoms arising nearer to death (although sensitivity analysis lessens this concern).
- The diagnoses occurred prior to the wars in Iraq and Afghanistan, with unclear generalizability of results to a more recent cohort.





Conclusions

Results add to a small but growing literature indicating subadditive risk of mental disorders in suicidal behavior (Flensburg-Madsen et al., 2009; Nock et al., 2009; Zhang et al., 2012).

Although two disorders generally confers more risk than one, results do not suggest that clinicians and policy makers should assign added weight to a second diagnosis, and indeed the added risk may be less than expectation.

A likely explanation for subadditivity is that the etiologic and phenotypic overlap between mental disorders (Kendler et al., 2011; Rzhetsky et al., 2007) creates some redundancy in risk for suicide with an additional diagnosis.





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