The relationship between suicide and violence in schizophrenia: Analysis of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) dataset

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ABSTRACT

Background: Suicide and violence often co-occur in the general population as well as in mentally ill individuals. Few studies, however, have assessed whether these suicidal behaviors are predictive of violence risk in mental illness.
Aims: The aim of this study is to investigate whether suicidal behaviors, including suicidal ideation, threats, and attempts, are significantly associated with increased violence risk in individuals with schizophrenia.
Method: Data for these analyses were obtained from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial, a randomized controlled trial of antipsychotic medication in 1460 adults with schizophrenia. Univariate Cox regression analyses were used to calculate hazard ratios (HRs) for suicidal ideation, threats, and attempts. Multivariate analyses were conducted to adjust for common confounding factors, including: age, alcohol or drug misuse, major depression, antisocial personality disorder, depression, hostility, positive symptom, and poor impulse control scores. Tests of discrimination, calibration, and reclassification assessed the incremental predictive validity of suicidal behaviors for the prediction of violence risk.
Results: Suicidal threats and attempts were significantly associated with violence in both males and females with schizophrenia with little change following adjustment for common confounders. Only suicidal threats, however, were associated with a significant increase in incremental validity beyond age, diagnosis with a comorbid substance use disorder, and recent violent behavior.
Conclusions: Suicidal threats are independently associated with violence risk in both males and females with schizophrenia, and may improve violence risk prediction.

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1. Introduction

Schizophrenia is associated with significantly elevated rates of both suicide (Harris and Barraclough, 1997; Palmer et al., 2005; Saha et al., 2007) and violence (Fazel et al., 2009a,b) compared to general population rates. Although suicide and violence have historically been viewed as distinct outcomes (Nock and Marzuk, 2000), several studies have shown that suicide and violence often co-occur, both in the general population (Kennedy et al., 1999; Conner et al., 2001; Christoffersen et al., 2005) and in mentally ill persons (Tardiff and Sweillam, 1980a,b; Plutchik et al., 1986; Convit et al., 1988; Feinstein and Plutchik, 1990; Apter et al., 1993; Asnis et al., 1994; Botsis et al., 1994; Apter et al., 1995), including in those with psychosis (Cheng et al., 1990; Hunt et al., 2006; Suokas et al., 2010). Most of this research, however, is based on cross-sectional studies and is dated. Closer scrutiny of this association using longitudinal designs is therefore necessary.

While previous work suggests that suicide may be more closely associated with violent behavior in schizophrenia as compared to other psychiatric disorders (Hunt et al., 2006), less work has investigated the association between suicidality and violence in these individuals. Attempts to address this question, moreover, have not provided clear evidence of a significant association as two systematic reviews have reached divergent conclusions regarding whether violence predicts suicide in those with schizophrenia (Hawton et al., 2005; Montross et al., 2005).

We have therefore investigated the longitudinal association between suicidality and violence in schizophrenia using the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) dataset, a nationally representative sample of 1460 participants with schizophrenia treated under usual care conditions between 2001 and 2004. We also investigated whether the association between violence and suicidality is bi-directional by conducting two separate analyses in which violence

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and suicidal behaviors were treated as separate outcomes. Additionally, as violence and suicidality are known to share many common risk factors (Conner et al., 2001), including: age (Conner et al., 2001), alcohol misuse (Greenwald et al., 1994; Conner et al., 2001), symptoms of depression (Apter et al., 1993), a diagnosis of antisocial personality disorder (Verona et al., 2001), drug misuse (Greenwald et al., 1994), gender (Tardiff and Sweillam, 1980a; Webb et al., 2011), impulsivity (Apter et al., 1993), and positive symptomatology (Apter et al., 1993), we conducted multivariate analyses to investigate whether any of these potentially confounding factors moderates the association between suicide and violence in schizophrenia.

2. Method

The data used in this study were collected as part of the National Institute of Mental Health's (NIMH) CATIE study. The details of this study have been reported elsewhere (Stroup et al., 2003, 2010). Briefly, the CATIE project was a multi-phase randomized controlled trial which compared the effectiveness and tolerability of first versus second generation antipsychotic medications (Stroup et al., 2003, 2010).

Between January, 2001 and December, 2004, 1493 males and females diagnosed with schizophrenia were recruited to participate in the CATIE project (Perlick et al., 2010). Due to concerns over quality, however, data from one site ($n = 33$) were excluded, leaving a total sample of 1460 participants. The present study is therefore based on information from these 1460 participants.

The project consisted of four phases. In the first, individuals were randomized to treatment with the typical antipsychotic perphenazine or one of three atypical antipsychotics: olanzapine, quetiapine, or risperidone (Stroup et al., 2003, 2010). Subsequent to Food and Drug Administration (FDA) approval in February 2001, participants could also be randomized to treatment with ziprasidone (Stroup et al., 2003, 2010). Only participants with a history of tardive dyskinesia were ineligible for randomization to perphenazine (Stroup et al., 2003, 2010). In phase 1B, individuals who refused or discontinued treatment with perphenazine in phase 1 of the CATIE project were randomly reassigned to treatment with olanzapine, quetiapine, risperidone, or ziprasidone (Stroup et al., 2003, 2010).

In phase 2 of the project, participants who had refused or discontinued any trial medication in phase 1 or 1B due to a lack of effect were prescribed either open-label treatment with clozapine, or, were randomized to treatment with olanzapine, quetiapine, risperidone, or ziprasidone (Stroup et al., 2003, 2010). On the other hand, participants who had refused or discontinued any medication due to the development of intolerable side-effects were randomized to olanzapine, risperidone, quetiapine, or ziprasidone (Stroup et al., 2003; Citrome and Stroup, 2006; Stroup et al., 2006; Swartz et al., 2008; Stroup et al., 2010). Lastly, in phase 3 of the project, participants who had refused or discontinued medications at any point in the trial could receive treatment with one of eight open-label medications, or with a combination of any two of these medications (Stroup et al., 2003, 2009; van der Oord et al., 2009; Stroup et al., 2010).

While the primary outcome of the CATIE trial was treatment discontinuation for any reason (Stroup et al., 2003, 2010), as part of the trial participants underwent frequent and detailed clinical assessments enabling information to be collected on a number of secondary outcomes, including the occurrence of adverse events such as suicide and violence (Stroup et al., 2009). The clinical data are widely available via the controlled-access repository of the NIMH (van der Oord et al., 2009).

2.1. Violence

As previous work suggests that reliance on self-reported incidents may cause the true extent of violence in this population to be underestimated (Swanson et al., 2006), for the purposes of this study violence was ascertained from the follow-up family interviews.

To identify whether risk factors for suicidality are predictive of violence in individuals with schizophrenia, only reports of violence perpetration made from the date of the six-month interview onward were coded for information regarding violent behavior. Additionally, where an individual had more than one positive report of violence, we coded violence from the report made closest to the end of the follow-up period. This ensured that the violent episode was more likely to have occurred when the participant was stabilized on one of the trial medications which, in turn, minimizes the impact of treatment non-adherence as a potentially confounding factor in any association.

2.2. Suicidality phenomena

Three suicidal phenomena were examined: ideation, threats, and attempts. In line with the Centers for Disease Control (CDC) uniform definitions (Crosby et al., 2011), suicidal ideation was defined as thoughts of engaging in suicidal behavior with or without a definitive plan but with no evidence of current suicidal behavior. A positive rating of suicidal ideation was coded from a rating of 'mild' or 'moderate' on the suicide item of the Calgary Depression Rating Scale (CDRS; Addington et al., 1993) or from a record of suicidal ideation on the CATIE Serious Adverse Events (SAE) record form.

Although use of the term suicidal threat is discouraged by the CDC uniform definitions, this term was preserved in the current study to reflect that adopted by the original CATIE trial authors. Suicidal threats were coded from family informant information provided at either the baseline or six monthly follow-up interviews.

Suicide attempt is defined by the CDC as non-fatal behavior with the potential for injury or death coupled with suicidal intent (Crosby et al., 2011). Suicide attempts were coded from a rating of 'severe' on the suicide item of the CDRS, a positive response on the baseline or follow-up family interview, or from the SAE record form. Overdose was coded from the SAE record form, while deliberate self-harm was coded from the baseline or follow-up family interview and from the SAE record form.

2.3. Potential confounding factors

A number of baseline demographic factors were investigated for their effect on the association between suicidal behavior and violence, including: age, duration of illness, health insurance status (as a proxy for socio-economic status), non-White ethnicity, educational status, and number of prior psychiatric admissions. Information on these factors was extracted from the CATIE screening questionnaire.

Alcohol misuse was coded from a clinician rating of alcohol abuse, dependence, or dependence necessitating inpatient care according to the Clinical Global Impression Scale (CGIS; Guy, 1976), a family report of excessive alcohol use at the baseline or follow-up interview, a record of alcohol abuse or dependence according to the SCID, or from a record of alcohol abuse or dependence according to the screening questionnaire.

Drug misuse was similarly coded from the CGIS, a family report of drug use at the baseline or follow-up interview, a record of abuse or dependence according to the SCID, or from the screening questionnaire. A positive test for cocaine, opiates, phencyclidine, methamphetamines, or cannabis according to hair strand analysis was also included as evidence of drug misuse.

Depression was coded continuously, from total scores on the CDRS, and categorically from the SCID or the screening questionnaire. A lifetime diagnosis of Antisocial Personality Disorder (ASPD) was coded from the screening questionnaire.

Positive symptomatology, hostility, and poor impulse control scores were coded from the Positive and Negative Symptom Scale (PANSS; Kay et al., 1987). As the PANSS was administered at several different time points throughout the CATIE trial (Stroup et al., 2010), scores were coded at both baseline and at six month follow-up. At baseline, participants had not yet entered the CATIE project. Therefore scores

on these measures are likely to reflect levels of symptomatology when medication adherence was not being monitored. After six months of participation, however, medication adherence had been monitored and therefore scores on these measures are likely to reflect each individual's highest level of functioning.

2.4. Statistical analyses

Individuals were followed from baseline until a positive rating for violence, withdrawal from the study, death, or end of the follow-up period (December 4, 2004). To determine whether the association was bi-directional, violence was also investigated as an exposure. In this analysis, individuals were followed from baseline until observance of suicidal phenomena, withdrawal, death, or the end of the follow-up period (December 4, 2004).

Cox regression was used to investigate both associations. Cox regression generates hazard ratios (HRs) and accompanying 95% confidence intervals (CIs) which represent the ratio of the event rate. The proportional hazards assumption was assessed visually using plots of the smoothed Schoenfeld residuals. Proportionality was inferred as present when the line formed by these residuals was roughly horizontal (Kleinbaum and Klein, 2012). Using this approach, there was no strong evidence that the proportionality assumption was violated for any of risk factors investigated.

Univariate associations were calculated separately for males and females. Multivariate associations were then calculated to investigate whether any association between violence and suicidal ideation, threats, and attempts was modified by age, alcohol or drug misuse, a lifetime diagnosis of major depression, a lifetime diagnosis of ASPD, depression scores, hostility scores, positive symptoms scores, or poor impulse control scores.

In addition to being significantly associated with the outcome of interest, an important risk factor must also demonstrate improvement in discrimination, calibration, and reclassification (Ioannidis and Tzoulaki, 2010). Discrimination, which refers to the ability of a model to distinguish between those who do and do not experience the event of interest, was assessed using Harrell's c-index (Pencina and D'Agostino, 2004). The c-index varies from 0.5 to 1.0, with 1.0 suggesting perfect discrimination (Wood and Greenland, 2009). The c-index has a similar interpretation to the area under the receiver operating curve (AUC) but is more appropriate for survival data characterized by censored observations (Nead et al., 2013). Calibration, which examines goodness of fit, was assessed statistically using the Grønnesby and Borgan test (Grønnesby and Borgan, 1996). Change in Royston's R^2 was used to assess reclassification, which refers to the ability of a novel risk factor to improve the percentage of variance explained by the risk model (Royston and Sauebrei, 2004; Royston, 2006).

In incremental predictive validity analyses, all risk factors were adjusted for age, a lifetime diagnosis for a substance use disorder (SUD), and previous violence. These factors were chosen as they have been previously shown to be strongly associated with violence risk in those with schizophrenia (Swanson et al., 2006; Fazel et al., 2009a,b). All analyses were conducted using Stata, version 11 (StataCorp, 2007).

3. Results

There were 1080 (73.9%) males and 380 (26.0%) females. Mean age at randomization was 40.6 yr (SD = 11.1, range 18 to 67). All participants were diagnosed with schizophrenia according to DSM-IV criteria, and were typically moderately ill (Caroff et al., 2010). Further demographic information is available in Table 1.

3.1. Suicidal behavior as a risk factor for violence

The median length of follow-up was 15.7 months (Inter-quartile range [IQR] 4.6 to 16.8). Around half (n = 666; 45.6%) withdrew from the CATIE study before all 18 months of follow-up had been completed. Five (0.3%) participants died during the analysis period: 2 from suicide, and one each from cardiac arrest, convulsions, and hypertensive heart disease.

A total of 121 (8.3%) participants were rated as violent at least once during the CATIE trial. The majority of these individuals were male (n = 97; 80.1%; females n = 24; 19.9%). With regard to the suicidality factors investigated, 493 (33.7%) experienced suicidal ideation, 162 (11.1%) threatened suicide, and 85 (5.8%) attempted suicide.

In univariate analyses, two suicidality factors were significantly associated with violence in males: suicidal threats (HR = 3.8, 95% CI 2.4–6.0) and attempts (HR = 2.8, 95% CI 1.5–5.4). For females, suicidal threats (HR = 9.4, 95% CI 4.0–21.6) and attempts (HR = 4.4, 95% CI 1.5–12.7) were also significantly associated with violence. In neither gender, however, was suicidal ideation significantly associated with violence (Table 2).

In relation to the potential confounders, a total of 485 (33.2%) participants had a history of alcohol misuse (males: n = 407, 37.6%; females: n = 78, 20.5%), 709 (48.5%) had a history of misusing drugs (males: n = 564, 52.2%; females: n = 145, 38.1%), 420 (28.7%) had a lifetime diagnosis of major depression (males: n = 291, 26.9%; females: 129, 33.9%), and 17 (1.1%) were diagnosed with ASPD (males: n = 15, 1.3%; females: n = 2, 0.5%). Adjustment for these factors did not materially change the associations between suicidality and violence for males or females (Table 3).

There were also no material changes to the associations between suicidality and violence following adjustment for age, baseline depression, hostility, positive symptomatology, or poor impulse control scores in either gender (Table 4). Additionally, no difference was found following adjustment for six month scores on these measures for females. However, adjustment for six month scores did cause the association between suicidal attempts and subsequent violence to become non-

Table 1
Demographic and clinical characteristics of the CATIE population measured at randomization.

Demographic and clinical characteristics measured at baseline	Gender			
	Males		Females	
	Mean	SD	Mean	SD
Age (years)	40.0	11.3	42.2	10.3
	Median	IQR	Median	IQR
Number previous psychiatric admissions over lifetime	4	(2.0–4.0)	3	(1.0–4.0)
Duration of illness (years)[1]	13	(4.0–23.0)	13	(5.5–21.0)
	N	%	N	%
Non-White ethnicity (yes/no)	403	37.3	181	47.8
Health insurance status (Medicare or Medicaid/Private)	974	91.3	333	89.8
Not completed high school education (yes/no)	266	24.6	108	28.4

Note: SD = standard deviation; IQR = interquartile range.
[1] Measured as the number of years between first prescription for any antipsychotic medication until randomization into the CATIE trial.

Table 2
Univariate hazard ratios (HRs) for the risk of violent behavior in males and females with schizophrenia.

Gender	Risk factor	n Violent		n Non-violent		HR (95% CI)	z	p
		With	Without	With	Without			
Males								
	Suicidal ideation	34	63	321	662	1.0 (0.7–1.5)	0.1	
	Suicidal threats	31	66	79	904	3.8 (2.4–6.0)	5.9	***
	Suicide attempt	13	84	47	936	2.8 (1.5–5.4)	3.2	**
Females								
	Suicidal ideation	4	20	134	222	0.3 (0.1–1.2)	−1.7	
	Suicidal threats	14	10	38	318	9.4 (4.0–21.6)	5.2	***
	Suicide attempt	5	19	20	336	4.4 (1.5–12.7)	2.8	**

Note:
*** Significant to the 0.001 level.
 ** Significant to the 0.01 level.
  * Significant to the 0.05 level.

significant for males (Table 4). Lastly, none of the baseline characteristics assessed, including: duration of illness, health insurance status, non-White ethnicity, educational status, and number of prior psychiatric admissions, materially changed the association between suicidal behavior and violence either gender (Table S1).

For both males and females, a previous suicidal threat was associated with the largest increase in both Harrell's c-index and Royston's R^2, suggesting that the addition of suicidal threats to a baseline risk model comprising age, comorbid SUD, and previous violence improves the prediction of subsequent violence. This adjusted model was also well calibrated, as indicated by a non-significant Grønnesby–Borgan test, suggestive of good fit (Table 5).

3.2. Violent behavior as a risk factor for suicidal phenomena

The median length of follow-up for this analysis was 10.8 months (IQR 2.8 to 16.6). Again, around half of the sample withdrew prior to successful completion of the full 18 month follow-up period (n = 698; 47.8%). Three (0.2%) participants died during this analysis period: one each from hypertensive heart disease, convulsions, and suicide.

Suicidal ideation, threats, or attempts were observed in 470 (32.2%) participants. Suicidal participants were mostly male (n = 331, 70.4%; females: n = 139, 29.5%). With regard to violence, 196 (28.8%) participants were rated by a family member as having behaved violently. Univariate analyses showed no association between a history of violence and subsequent suicidal phenomena in males (HR = 1.3, 95% CI 0.9–1.8, p = 0.10) or females (HR = 1.0, 95% CI 0.6–1.6, p = 0.93).

4. Discussion

The longitudinal association between suicidality and violent behavior was investigated in 1460 participants diagnosed with schizophrenia, recruited between 2001 and 2004 as part of the NIMH CATIE project. Strong associations with violence were found for suicidal threats and attempts in both males and females. Suicidal ideation, however, was not associated with violence in either this study or in a previous meta-analysis of risk factors for violence in psychosis (Witt et al., 2013). One reason may be that suicidal ideation is extremely common in this population (Kontaxakis et al., 2004). Alternatively it may be that while violence is associated with more behavioral forms of suicidality, such as attempted suicide, it is not related to suicidal ideation, as has previously been shown in prisoner populations (Sarchiapone et al., 2009; Zhang et al., 2010). In line with this, recent work suggests that impulsivity could mediate the association between suicidal behavior and violence, thereby explaining why impulsive suicidal behaviors, such as attempted suicide, are more strongly associated with violence risk than suicidal ideation (Witt et al., 2013).

Furthermore, although previous work suggests that confounding factors such as age, alcohol misuse, anger and/or hostility, ASPD, major depression, and drug misuse may account for the association between violence and suicidality, in multivariate analyses we found no evidence that these factors confounded the relationship in either gender. With regard to confounding factors measured continuously, while adjustment for baseline depression, hostility, positive symptom, and impulse control scores resulted in no material changes to the associations for males or females, adjustment for six month scores on these measures

Table 3
Multivariate hazard ratios (aHRs) for the risk of violent behavior in males and females with schizophrenia adjusted for categorical confounding factors.

Gender	Risk factor	Alcohol misuse	Drug misuse	Diagnosis of MDD	Diagnosis of ASPD	Any comorbidity
		aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Males						
	Suicidal ideation	0.9 (0.6–1.4)	0.9 (0.6–1.4)	1.0 (0.6–1.5)	1.0 (0.7–1.5)	0.9 (0.6–1.4)
	Suicidal threat	3.4 (2.2–5.3) ***	3.9 (2.5–6.1) ***	3.8 (2.4–6.0) ***	3.8 (2.4–6.0) ***	3.8 (2.5–5.9) ***
	Suicide attempt	2.8 (1.5–5.4) **	2.8 (1.5–5.4) **	2.8 (1.4–5.4) **	2.8 (1.5–5.3) **	2.8 (1.5–5.4) **
Females						
	Suicidal ideation	0.3 (0.1–1.1)	0.3 (0.1–1.1)	0.3 (0.1–1.2)	0.3 (0.1–1.2)	0.3 (0.1–1.1)
	Suicidal threat	8.6 (3.7–19.8) ***	9.4 (4.0–21.8) ***	9.3 (3.9–21.9) ***	9.3 (4.0–21.5) ***	9.4 (4.0–21.9) ***
	Suicide attempt	4.0 (1.4–11.3) **	4.3 (1.4–12.7) **	4.5 (1.5–13.2) **	4.4 (1.5–12.6) **	4.4 (1.5–12.9) **

Note: MDD = Major Depression Disorder; ASPD = Antisocial Personality Disorder; Any comorbidity = diagnosed with any one of these four comorbid conditions.
*** Significant to the 0.001 level.
 ** Significant to the 0.01 level.
  * Significant to the 0.05 level.

Table 4
Multivariate hazard ratios (aHRs) for the risk of violent behavior in males and females with schizophrenia adjusted for continuous confounding factors.

Gender	Risk factor	Age (years)	Depression scores (baseline)	Depression scores (6 months)	Hostility scores (baseline)	Hostility Scores (6 months)	Positive symptom scores (baseline)	Positive symptom scores (6 months)	Poor impulse control scores (baseline)	Poor impulse control scores (6 months)
		aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Males										
	Suicidal ideation	1.0 (0.6–1.5)	0.9 (0.5–1.4)	0.8 (0.4–1.5)	0.9 (0.6–1.4)	1.0 (0.6–1.8)	0.9 (0.6–1.5)	1.1 (0.7–1.9)	0.9 (0.6–1.4)	1.1 (0.7–1.9)
	Suicidal threat	3.2 (2.0–5.2)***	3.8 (2.4–6.1)***	3.0 (1.7–5.4)***	3.9 (2.5–6.1)***	3.6 (2.0–6.4)***	3.8 (2.4–6.0)***	3.2 (1.8–5.8)***	3.9 (2.5–6.2)***	3.5 (1.9–6.2)***
	Suicide attempt	2.1 (1.1–4.1)*	2.8 (1.4–5.5)**	2.1 (0.8–5.2)	3.0 (1.6–5.6)**	2.3 (0.9–5.6)	2.9 (1.5–5.5)**	2.3 (0.9–5.4)	2.9 (1.5–5.6)**	2.4 (0.9–5.6)
Females										
	Suicidal ideation	0.3 (0.1–1.2)	0.4 (0.1–1.7)	0.2 (0.1–1.2)	0.3 (0.1–1.2)	0.3 (0.1–1.4)	0.3 (0.1–1.1)	0.3 (0.1–1.2)	0.3 (0.1–1.1)	0.3 (0.1–1.2)
	Suicidal threat	8.4 (3.5–19.8)***	10.7 (4.5–25.5)***	15.6 (5.2–46.9)***	10.0 (4.1–24.0)***	13.6 (4.7–39.1)***	9.1 (3.7–22.4)***	12.3 (4.2–35.9)***	9.6 (4.0–22.9)***	12.4 (3.9–39.9)***
	Suicide attempt	4.1 (1.4–11.6)**	5.3 (1.8–15.9)**	5.7 (1.8–18.3)**	4.3 (1.4–13.1)**	5.2 (1.4–19.2)*	4.2 (1.4–12.7)*	5.0 (1.6–15.8)**	4.5 (1.5–13.3)*	5.4 (1.6–17.6)**

Note:
*** Significant to the 0.001 level.
** Significant to the 0.01 level.
* Significant to the 0.05 level.

resulted in some moderation of the association between suicidal attempts and violence in males. We suggest that this finding implies that levels of symptomatology while compliant with medication may be an important predictor of violence risk. Adjusting for other baseline factors, including duration of illness, health insurance status, non-White ethnicity, educational status, and number of prior psychiatric admissions, also did not moderate the association between suicidal behavior and violence in this population.

Reclassification analyses reveal that the addition of suicidal threats increases Royston's R^2 by 13.4% in males and 44.1% in females. Change in discrimination, as measured by Harrell's c-index, was significant for men, and approached significance in women. Few violence risk assessment instruments currently include an assessment of suicidal behavior, however (Witt et al., 2013). Results of this study therefore suggest that the inclusion of an item assessing threatened suicide should be considered for existing violence risk assessment instruments.

It is unclear whether the association between threatened suicide and violence is specific to schizophrenia, however. We therefore conducted a systematic review of the PUBMED database covering the last 5 years (1 January, 2009 to 31 December, 2013) and found no other work that addressed the association between threatened suicide and risk of violence perpetration. Further work on this question is therefore necessary.

A history of violent behavior was not significantly associated with suicidal phenomena in either gender, in line with findings of earlier meta-analyses of factors associated with risk of suicidal behavior in people with schizophrenia (Hawton et al., 2005), but in contrast with those of another systematic review (Montross et al., 2005). The association with completed suicide, however, could not be examined due to a lack of statistical power. Previous epidemiological work, however, suggests a significant association between criminal history and completed suicide in the general population (Webb et al., 2011).

4.1. Implications

Two implications follow from these findings. First, as part of the clinical risk assessment of violence in schizophrenia, as recommended by clinical guidelines in both the US and UK, a careful examination of history of suicidality should be included. Second, the association between suicidal attempts and violence may be modified by six month depression, hostility, positive symptomatology, and poor impulse control scores in males. Given that medication adherence was monitored during the CATIE trial, this finding may suggest that acute symptomatology, perhaps exacerbated by medication non-adherence, may account for some of the association between suicidality and violence in males. Previous work has, for example, shown that treatment non-adherence is significantly associated with increased suicide (Hawton et al., 2005) and violence (Witt et al., 2013) risk in this population. Efforts to improve medication adherence may therefore lead to a reduction in both behaviors.

4.2. Strengths

A variety of measures were used to assess exposure to suicidality and violence in this study, including a combination of both self-report, informant report, and psychometric tools. Given the limitations inherent in self-report and informant-report data in isolation, the use of both data sources in combination may have led to a more accurate indication as to the extent of both suicidality and violence in this study compared to previous investigations.

Secondly, few exclusion criteria were used to prevent participation of sub-groups of schizophrenia patients who are often excluded from other RCTs, including those with treatment refractory disorders, those who had experienced multiple symptomatic exacerbations, those with a history of medication non-adherence (Hofer et al., 2000), and those with comorbid conditions, or substance misuse (Gilbody et al., 2002).

Table 5
Multivariate hazard ratios (aHRs) and incremental predictive validity analyses for the risk of violent behavior in males and females with schizophrenia.

Gender	Risk factor	aHR (95% CI)	z	p	Harrell's c-index			Grønnesby–Borgan χ^2 test				Adjusted Royston's R^2	
					% (95% CI)	Δ (%)	p	χ^2	p	$\Delta\chi^2$	Δp	% (95% CI)	Δ (%)
Males													
	Baseline model				70.2 (65.7–74.7)			10.9	**			22.2 (12.6–34.9)	
	+ Suicidal threats	3.4 (2.1–5.6)	5.0	***		+5.3	**			−8.6	+0.13		+13.4
	+ Suicidal attempts	2.3 (1.1–4.7)	2.3	*		+1.5				−6.6	+0.14		+2.9
Females													
	Baseline model				67.3 (62.0–72.7)			1.6	0.20			26.7 (3.7–82.4)	
	+ Suicidal threats	10.4 (4.2–25.7)	5.1	***		+3.3				−1.6	+0.71		+44.1
	+ Suicidal attempts	4.1 (1.5–11.4)	2.8	**		+0.6				−1.6	+0.70		+10.3

Note: Baseline model composed of age at randomization, diagnosis of comorbid substance use disorder, and recent violent behavior in the six months preceding randomization to the CATIE project. Change in Harrell's c-index, the Grønnesby–Borgan χ^2 test, and adjusted Royston's R^2 is assessed with reference to this baseline model. The overall Harrell's c-index, Grønnesby–Borgan χ^2 test, and adjusted Royston's R^2 is calculated for the baseline model alone.
*** Significant to the 0.001 level.
** Significant to the 0.01 level.
* Significant to the 0.05 level.

4.3. Limitations

Previous research does, however, suggest that RCTs of antipsychotic effectiveness in schizophrenia are less likely to recruit individuals reporting thoughts of suicidality and deliberate self-harm (Gilbody et al., 2002). Consequently, the results of this study may not generalize to all patients with schizophrenia. Nevertheless, the CATIE trial used wide inclusion criteria to recruit a diverse range of participants treated under usual care conditions (Stroup et al., 2003).

Second, the CATIE data were not collected specifically to meet the aims of this study. Therefore, a number of potentially relevant confounding factors could not be included in the multivariate analyses, including intelligence scores (Webb et al., 2011) and neighborhood socioeconomic deprivation (Kennedy et al., 1999). Additionally, although previous work identifies anger and impulsivity as potential confounders (Apter et al., 1993), these factors were not specifically assessed. Instead, anger and impulsivity had to be coded from the hostility and poor impulse control items of the PANSS. Previous work, however, suggest that impulsivity consists of both a behavioral and cognitive component (Winstanley et al., 2006; Broos et al., 2012). The impulse control item on the PANSS, in contrast, reflects only the behavioral component of impulsivity. Further research should determine whether measures which reflect the cognitive component of impulsivity may account for the association between suicidality and violence.

Anger and hostility also appear to be conceptually distinct (Eckhardt and Barbour, 1997). Whereas anger reflects an emotion elicited by circumstances, hostility implies a cognitive belief concerning the intentions of others (Sanz et al., 2010). Future work is therefore necessary to determine whether it is the emotional component of anger which underlies any association between suicidality and violence.

Lastly, around half of the participants originally enrolled in the CATIE trial withdrew before all 18 months of follow-up were completed. Adjusting for completion status did not materially affect the association between suicidal threats and violence in this study, however (results not shown). Additionally, work indicates that loss to follow-up was similar between treatment groups in the CATIE trial (Rosenheck and Leslie, 2010).

4.4. Conclusions

This study demonstrated that suicidal threats and attempts where significantly associated with an increased risk of violent behavior in a sample of 1460 males and females with schizophrenia. Suicidal ideation, however, was not significantly associated with violence. When analyses were adjusted for alcohol misuse, drug misuse, major depression, or

ASPD, the association was not materially different. Similarly, when hazards for violence were adjusted for age, depression, hostility, positive symptomatology, or poor impulse control scores, there was little change in the association between suicidal ideation, threats, or attempts and violence. Results of this study therefore suggest that certain suicidal behaviors, and suicidal threats in particular, may represent an independent risk factor for violence in schizophrenia.

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