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Prospective Study of
Clinical Predictors of
Suicidal Behavior.

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El trabajo de investigación presentado por **Dña. María Antonia Oquendo Villar**, titulado ***“Predictores clínicos de conducta suicida. Abordaje prospectivo”*** realizado bajo mi dirección, reúne los requisitos científicos, metodológicos y de originalidad suficientes para ser defendido como Tesis Doctoral ante el Tribunal que legalmente proceda.

Y para que surta los efectos oportunos, se firma la presente en Madrid a treinta de agosto de 2010.

Dr. Enrique Baca García

A handwritten signature in black ink, appearing to read 'EBG', is placed above the printed name of the doctor.

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1	RESUMEN.....	15
2	OVERALL THESIS ABSTRACT.....	17
3	INTRODUCCIÓN.....	19
	3.1 Definición de la Conducta Suicida.....	19
	3.2 Epidemiología de las Conductas Suicidas.....	19
	3.3 La Conducta Suicida y el Trastorno Mental.....	19
	3.4 Introducción al Modelo Estrés-Diátesis de la Conducta Suicida.....	19
	3.5 Factores que Actúan como Estresores o Precipitantes.....	20
	3.5.1 Estresores Psicobiológicos.....	20
	3.5.2 Estresores Ambientales.....	20
	3.6 Factores de Riesgo que Afectan a la Diátesis.....	21
	3.6.1 Factores Neurobiológicos que Afectan a la Diátesis.....	21
	3.6.2 Factores Psicobiológicos que Afectan a la Diátesis.....	21
	3.6.3 Factores Ambientales que Afectan a la Diátesis.....	22
	3.7 Aproximaciones Terapéuticas.....	22
	3.7.1 Evaluación del Riesgo Suicida.....	23
	3.7.2 Psicoterapia de la Conducta Suicida.....	23
	3.7.3 Psicofarmacología de la Conducta Suicida.....	23
	3.7.4 Terapia Electroconvulsiva.....	23
	3.7.5 Intervención en Crisis.....	23
4	INTRODUCTION.....	25
	4.1 Definition of Suicidal Behavior.....	25
	4.2 Epidemiology of Suicidal Behavior.....	25
	4.3 Association of Suicidal Behavior with Psychiatric Diagnoses.....	25
	4.4 A Model for Understanding Suicidal Behavior: The Stress- Diathesis Model.....	26

4.5	Risk Factors Acting as Stressors or Precipitants.....	26
4.5.1	Psychobiological Stressors	26
4.5.2	Environmental Stressors	26
4.6	Risk Factors Affecting the Diathesis.....	27
4.6.1	Neurobiological Factors Affecting the Diathesis.....	27
4.6.2	Psychobiological Factors Affecting the Diathesis	27
4.6.3	Environmental Factors Affecting the Diathesis	28
5	RESEARCH ON SUICIDAL BEHAVIOR. STATE OF THE ART	29
5.1	Intervention Research for Suicidal Behavior.....	29
5.2	Period of Highest Risk.....	29
5.3	Risk Factors for Suicidal Behavior	29
5.3.1	Past Suicidal Behavior	29
5.3.2	Suicidal Ideation	30
5.3.3	Psychopathology	30
5.3.4	Psychiatric Comorbidity	31
5.3.5	Traits	32
5.3.6	Other Clinical Variables	32
6	OBJETIVES AND HYPOTHESES	33
6.1	OBJECTIVES.....	33
6.2	HYPOTHESES	33
6.2.1	Clinical Predictors of Suicidal Acts After a Major Depressive Episode in Affective Disordered Patients.....	33
6.2.2	Sex Differences in Clinical Predictors of Suicidal Acts After a Major Depressive Episode in Affective Disordered Patients.....	33
6.2.3	Adequacy of Antidepressant Treatment	34
6.2.4	Role of Life Events in Precipitating Suicidal Behavior.....	34
7	MATERIAL Y MÉTODOS	35

7.1 FUNDAMENTOS ÉTICOS DEL ESTUDIO	35
7.1.1 Implicaciones Éticas en la Investigación de la Conducta Suicida	35
7.1.2 Consentimiento Informado	35
7.1.3 Confidencialidad	35
7.2 DISEÑO DE LA INVESTIGACIÓN	35
7.2.1 Descripción del Diseño	35
7.3 Subjects	36
7.3.1 Clinical Predictors of Suicidal Acts After a Major Depressive Episode in Affective Disordered patients	36
7.3.2 Sex Differences in Clinical Predictors of Suicidal Acts After a Major Depressive Episode in Affective Disordered Patients	36
7.3.3 Adequacy of Antidepressant Treatment	36
7.3.4 Role of Life Events in Precipitating Suicidal Behavior	36
7.4 Instruments	37
7.4.1 Datos Sociodemográficos	37
7.4.2 Historia Médico-quirúrgica del Paciente y sus Familiares	37
7.4.3 Problemas Psicosociales y Ambientales	37
7.4.4 Escala de Evaluación de la Actividad Global (EEAG)	38
7.4.5 Valoración de Agresividad	38
7.4.6 Evaluación de Impulsividad	38
7.4.7 Valoración de la Conducta Suicida	38
7.4.7.1 Intencionalidad Suicida: Suicide Intent Scale (Beck y Kovacs 1979)	38
7.4.7.2 Letalidad	39
7.4.7.3 Otras Características de la Tentativa	39
7.4.7.4 Antecedentes Familiares de Conducta Suicida: Familiar Suicide History (Beck, Resnik, y Lettieri 1974)	39
7.4.7.5 Antecedentes Personales de Conducta Suicida	39
7.4.7.6 Factores Protectores	39
7.4.8 Valoraciones Prospectivas Durante el Periodo de Seguimiento	39

7.4.8.1	Assessment of Adequacy of Antidepressant Treatment	39
7.4.8.2	Assessment of Life Events.....	40
7.5	Statistical Method	40
7.5.1	Cross-Sectional Analysis of Baseline Characteristics	40
7.5.2	Analysis of Clinical Predictors of Suicidal Acts After a Major Depressive Episode in Affective Disordered Patients.....	40
7.5.3	Analysis of Sex Differences in Clinical Predictors of Suicidal Acts After a Major Depressive Episode in Affective Disordered Patients.....	41
7.5.4	Analysis of Prospective Data to Determine the Adequacy of Antidepressant Treatment	41
7.5.5	Analysis of Prospective Data to Determine the Role of Life Events in Precipitating Suicidal Behavior.....	41
8	RESULTS.....	43
8.1	Descripción Muestral	43
8.1.1	Sociodemográficos.....	43
8.1.2	Diagnósticos Psiquiátricos.....	43
8.1.3	Puntuaciones en las Escalas de Impulsividad y Agresividad	44
8.1.4	Puntuaciones en las Escalas de Pesimismo y Suicidio	44
8.2	Clinical Predictors of Suicidal Acts After a Major Depressive Episode in Affective Disordered Patients.....	44
8.2.1	Baseline Clinical Analysis.....	44
8.2.2	Prospective Clinical Predictors Analysis.....	45
8.2.3	Diathesis and Future Suicidal Behavior.....	46
8.3	Sex Differences in Clinical Predictors of Suicidal Acts after a Major Depressive Episode in Affective Disordered Patients	47
8.3.1	Baseline Characteristics of Subjects.....	47
8.3.2	Follow-Up of Men and Women: Univariate Analyses	48
8.3.3	Follow-Up of Men and Women: Multivariate Analyses	49
8.4	Adequacy of Antidepressant Treatment.....	49

8.5 Role of life events in precipitating suicidal behavior	51
8.5.1 Baseline Clinical Characteristics	51
8.5.2 Prospective Clinical Predictors	51
9 DISCUSSION	53
9.1 Hypothesis contrast.....	53
9.1.1 Clinical Predictors of Suicidal Acts after a Major Depressive Episode in Affective Disordered patients.....	53
9.1.2 Sex Differences in Clinical Predictors of Suicidal Acts after a Major Depressive Episode in Affective Disordered Patients.....	55
9.1.2.1 Risk Factors for Men	55
9.1.2.2 Risk Factors for Women	56
9.1.2.3 Risk Factors Affecting Men and Women	56
9.1.3 Adequacy of Antidepressant Treatment	57
9.1.4 Role of Life Events in Precipitating Suicidal Behavior.....	58
9.1.4.1 Positive and Negative Stressors	58
9.1.4.2 Type of Stressors: Health Related Stressors as Precipitants	59
9.1.4.3 The Predictive Capacity of Baseline Pessimism and Aggression/ Impulsivity Factors	59
9.2 Relevance	59
9.2.1 Clinical Predictors of Suicidal Acts After a Major Depressive Episode in Affective Disordered Patients.	59
9.2.2 Sex Differences in Clinical Predictors of Suicidal Acts After a Major Depressive Episode in Affective Disordered Patients.....	60
9.2.3 Adequacy of Antidepressant Treatment	60
9.2.4 Role of Life Events in Precipitating Suicidal Behavior.....	60
9.3 Limitations	60
9.3.1 Methods	61
9.3.1.1 Data not Obtained	61
9.3.1.2 Bias	61
9.3.1.3 Analysis.....	61

9.4	New Hypotheses	61
9.5	Future Research.....	61
10	CONCLUSIONES.....	63
11	CONCLUSIONS	65
12	BIBLIOGRAFÍA.....	67
13	TABLAS	77
14	FIGURAS	79
15	APÉNDICES	81

1 RESUMEN

La conducta suicida es una de las principales causas de muerte prematura y pérdida de productividad. El sufrimiento asociado a esta conducta afecta no solo al individuo protagonista, también es un motivo de pesar para su familia y entorno social. Por si fuera poco, se trasmite a través de generaciones. Así, es clave identificar factores de riesgo y de protección que permitan desarrollar actividades preventivas a nivel individual.

Los estudios prospectivos son una de las estrategias más robusta de investigación para encontrar estos factores de riesgos y protección. En la presente tesis doctoral se muestran una serie de estudios prospectivos de pacientes con trastornos afectivos. Todos estos pacientes se evalúan al inicio del seguimiento desde el punto de vista psicopatológico, rasgos de personalidad, antecedentes personales y familiares y psicométrico. Se ha tratado de comprobar la capacidad de estas características para predecir la aparición de conductas suicidas en los 2 años de seguimiento. La predicción de la conducta suicida basada en la presentación inicial del paciente es esencial, ya que el clínico debe ser capaz de identificar los individuos con alto riesgo de suicidio en la entrevista clínica para poder planificar el tratamiento futuro. Sin embargo, el presente trabajo no acaba aquí: además se han analizado los cambios que experimentan tres parámetros clínicos básicos durante el periodo de seguimiento: 1) recurrencia de episodios depresivos, 2) experiencia de acontecimientos vitales, 3) tratamiento antidepresivo

Los datos indican que hay ciertos factores que pueden explicar la conducta suicida en pacientes con trastornos afectivos: antecedentes de conducta suicida previa, depresión subjetiva, fumar, pesimismo y agresividad. Se ha comprobado como el efecto del pesimismo y de la agresividad es aditivo. Se ha comprobado como hay importantes diferencias entre ambos sexos en el efecto de estos factores. El efecto de la depresión sobre la conducta suicida es claro pero curiosamente el papel de los acontecimientos vitales es nimio en la aparición de la conducta suicida. Aunque esperábamos encontrar un fuerte efecto protector de los tratamientos antidepresivos, la sorprendente escasez de pautas de tratamiento adecuadas no permitió detectar el efecto anticipado.

Este trabajo motiva preguntas sobre cómo se utilizan los tratamientos antidepresivos que requieren ensayos clínicos aleatorizados. En cuanto al efecto de los acontecimientos vitales sobre el suicidio, parece que es más importante la actitud del sujeto frente a ellos. Un tema pendiente en este trabajo es la valoración de las recaídas en el consumo de sustancias durante el seguimiento.

2 OVERALL THESIS ABSTRACT

Suicidal behavior is one of the most central causes of premature death and lost productivity. The suffering associated with this behavior is experienced not only by the afflicted individual, but also by their social support network and family. It is also transmitted across generations. Thus, identifying risk and protective factors that may permit preventive efforts at the individual level is key. One of the most robust strategies for finding such factors is prospective study. In this series of prospective studies, patients with Major Affective Disorder are thoroughly characterized at study entry in terms of psychopathology, symptomatology, character traits, family and personal history and many other parameters. These features are then examined in terms of their ability to predict the occurrence of suicidal behavior over a two-year period. But our work does not end there. Prediction based on the presenting clinical picture is essential, since the clinician needs to be able to identify individuals at risk in the clinical encounter so as to plan future treatment. However, key parameters change over the period of observation: (1) patients endure recurrence of depression; (2) patients experience life events; and (3) patients are exposed to antidepressant treatment. These critical variables must also be examined. The data suggests that several elements predict suicidal behavior among affectively disordered individuals. Past suicidal behavior, subjective depression, cigarette smoking, pessimism and aggression all play key roles, and for pessimism and aggression, the effects are additive. Yet, these effects are not uniform across sexes and we detected important differences. Strikingly, we found that the onset of a Major Depressive Episode increased the risk for suicidal behavior several fold, but life events appeared to have negligible effects on the occurrence of suicidal acts. Although we anticipated the detection of a strong protective effect of antidepressant medication treatment in mitigating risk for suicidal behavior, the rates of adequate treatment were so shockingly low that we could not detect the anticipated effect. Thus, we are left with questions about the utility of antidepressants which would require testing in a randomized controlled trial, about the effect of life events which may be more closely linked to the perception that the individual has about life events, and about the importance of unmeasured variables in this study such as relapse into substance abuse in the follow up period. This study answers several extant questions but raises many others, equally worthy of scientific pursuit.

3 INTRODUCCIÓN

Abstract

La conducta suicida puede entenderse como el resultado de la interacción entre un umbral individual para actuar sobre unas ideas suicidas y la presencia de estresores o desencadenantes de la conducta suicida. Clasificar los factores de riesgo en función de que afecten al umbral o sirvan como desencadenantes puede ayudar a entender como interactúan unos con otros y finalmente puede aportar nuevas estrategias de prevención de la conducta suicida. El tratamiento de la conducta suicida incluye una valoración exhaustiva del riesgo suicida y un plan terapéutico global que aborde la patología psiquiátrica del paciente y fije un calendario de visitas así como un plan en caso de crisis.

3.1 Definición de la Conducta Suicida

La conducta suicida engloba un espectro que incluye el suicidio consumado, el intento de suicidio y la ideación suicida. El suicidio supone la muerte auto-inflingida intencionalmente. El intento de suicidio se caracteriza por lesiones, cualquiera que sea la gravedad de las mismas, autoprovocadas con la intención de causar el propio fallecimiento. La ideación suicida son pensamientos sobre el deseo de finalizar la propia vida. Entre estas categorías existe un amplio rango de manifestaciones.

3.2 Epidemiología de las Conductas Suicidas

El suicidio es una causa frecuente de muerte en el mundo (La Vecchia y cols., 1994). La mortalidad por suicidio es diferente en distintos países, Hungría y Sri Lanka (52.12 y 49.62/100.000 respectivamente) tienen las tasas más altas, mientras Egipto presenta las más bajas (0.08/100.000). Los países latinoamericanos (incluyendo España) muestran unas tasas inferiores a 15.5/100.000. Algo similar ocurre con los intentos de suicidio. Un estudio realizado en 9 países ha documentado como la ideación y los intentos de suicidio eran más frecuentes en Puerto Rico, mientras que el Líbano era el país con menor incidencia.

Diversos factores sociodemográficos como la edad y el sexo influyen en la conducta suicida. Los intentos de suicidio son más frecuentes en mujeres que en hombres (2:1). En contraste, el suicidio consumado presenta una frecuencia inversa (hasta 1:3). Además, el suicidio consumado presenta una curva bimodal con un aumento de la incidencia en jóvenes y personas de la tercera edad. Como se ha comprobado antes, la conducta suicida está relacionada con factores étnicos y culturales.

3.3 La Conducta Suicida y el Trastorno Mental

Las autopsias psicológicas, método por el que el historial psiquiátrico de la víctima de suicidio se

reconstruye a partir de entrevistas con familiares, han demostrado que entre el 90 y el 95% de los fallecidos por suicidio sufrían al menos un trastorno mental. Esta tasa es muy significativa aún teniendo en cuenta las limitaciones de hacer un diagnóstico sin conocer al paciente. Por lo tanto, queda claro que la presencia de un trastorno mental es un factor crítico para el suicidio.

Los diagnósticos que más se han relacionado con el suicidio han sido la esquizofrenia, los trastornos afectivos y el alcoholismo. Se estima que el 10-15% de los pacientes con esquizofrenia fallecen por suicidio. Con respecto a los trastornos afectivos, los estudios revelan que entre el 2 y el 15% de los pacientes con depresión unipolar cometen suicidio. Evidentemente la cifra del 2% corresponde a pacientes con depresión unipolar en tratamiento ambulatorio, mientras el 15% corresponde a pacientes con depresión severa que requiere hospitalización. Quizás el trastorno afectivo con mayor riesgo sea el trastorno bipolar. De hecho, un meta-análisis revela que el 15-20% de estos pacientes fallece por suicidio.

La frecuencia de suicidio en trastornos por abuso de sustancias es alta, y se incrementa espectacularmente si existe comorbilidad con esquizofrenia, depresión o trastorno bipolar.

Finalmente, los pacientes con trastorno de personalidad tienen también un mayor riesgo de conducta suicida, especialmente el cluster B y dentro de ellos el trastorno límite (borderline) de personalidad. Con respecto a este trastorno existe un sesgo en la actitud de muchos clínicos, que presuponen en los pacientes con trastorno límite una actitud manipulativa relacionada con el suicidio. Hay que tener en cuenta que la frecuencia de suicidio en los pacientes con trastorno de personalidad límite oscila entre el 8 y 10%.

3.4 Introducción al Modelo Estrés-Diátesis de la Conducta Suicida

La mayoría de los estudios en suicidiología se han centrado en los factores precipitantes o estresantes. Como se ha visto antes, la presencia de un trastorno mental es un factor inequívoco en

la conducta suicida. Sin embargo, está claro que no todos los pacientes con trastornos mentales intentan o cometen suicidio.

con déficits serotoninérgicos. Como es sabido, uno de los hallazgos más replicados en la investigación en psiquiatría biológica, es la disminución en la función serotoninérgica en la conducta suicida.



Figura 1. Modelo Estrés-Diátesis.

Un modelo para explicar la relación entre los trastornos mentales y el suicidio es conceptualizar el riesgo como el resultado de otros factores y características del paciente que lo sitúan en el disparadero del pensamiento y acto suicida. Los factores de riesgo que están asociados con la conducta suicida tienen orígenes diversos (ver figura 1.). Algunos parecen estar relacionados con factores genéticos o hereditarios (Mann y cols., 1999a). Sin embargo, el suicidio aparece en familias independientemente de otras condiciones psicopatológicas hereditarias como los trastornos afectivos, esquizofrenia o abuso de alcohol (Brent y cols., 1996; Egeland y Sussex, 1985). Otros factores de riesgo están aparentemente ligados a factores ambientales como la disponibilidad de métodos letales o la ruptura de relaciones emocionales importantes.

En el modelo que proponemos (Mann y cols., 1999b), el suicidio es un resultado que requiere tanto un estresor como una diátesis. Por lo tanto, debe haber un factor precipitante o "gatillo" para que el suicidio ocurra, además de la diátesis o vulnerabilidad que la persona tiene para actuar en la dirección de los pensamientos suicidas. En este sentido, se ha incluido a la agresividad e impulsividad como factores relacionados con la vulnerabilidad para la conducta suicida, así como factores genéticos independientes de la herencia de los trastornos mentales, y experiencias tempranas traumáticas como maltrato y abuso sexual en la infancia. Se ha estudiado la relación entre los factores que afectan a la vulnerabilidad

3.5 Factores que Actúan como Estresores o Precipitantes

3.5.1 Estresores Psicobiológicos

Episodios de Trastorno Psiquiátrico. La presencia de un episodio agudo de depresión o psicosis puede ser un estresor o requisito necesario pero no suficiente para que ocurra el suicidio (Mann y cols., 1999b; Barraclough y cols., 1974; Isacson y cols., 1992).

Intoxicación Aguda por Sustancias. La intoxicación aguda a menudo juega un papel en el suicidio consumado. Puede ser un método empleado por la víctima para facilitar el acto, al tiempo que la intoxicación juega un papel desinhibidor que provoca que la persona ponga en práctica ideas que de otro modo ignoraría. Alrededor del 60% de los jóvenes toman sedantes o alcohol en el contexto del intento de suicidio. Además, las intoxicaciones agudas también tienen importantes efectos neurobiológicos que pueden incidir directamente en la conducta suicida, incluyendo una liberación aguda de serotonina y dopamina, seguida de una depleción relativa (Mann y cols., 1999a). Por tanto, la intoxicación aguda puede ser un detonante de la conducta suicida, con un papel complejo tanto como facilitadora como causante.

3.5.2 Estresores Ambientales

Mimetismo. El mimetismo o la imitación a menudo se ha postulado como causa cuando ocurren epidemias de suicidio especialmente entre jóvenes (Schmidtke y Häfner, 1988). El suicidio

de un adolescente en una comunidad puede facilitar la ocurrencia de conductas suicidas en individuos vulnerables como aquellos que están deprimidos o consumen drogas. Se ha especulado con la posibilidad de que la reciente publicidad sobre el suicidio asistido puede incrementar la tasa de suicidios consumados en ancianos. Más aun, los suicidios asistidos y la eutanasia probablemente contribuyen a infraestimar las tasas de suicidio (Diekstra, 1993). De esta forma, el mimetismo puede servir de desencadenante para la conducta suicida.

Crisis Familiares, Financieras o Sociales. Discordias familiares y dificultades en el trabajo se han descrito en la literatura como factores de riesgo para el suicidio consumado tanto en hombres como mujeres (Heikkinen y cols., 1994). Para los hombres, la presencia de problemas económicos puede incrementar el riesgo. En las mujeres el riesgo es mayor si han sufrido recientemente la pérdida de un familiar o un amigo cercano. Sin embargo, como éstos son estresores comunes y pueden estar asociados a trastornos psiquiátricos, su importancia adicional como detonantes de la conducta suicida es difícil de estimar.

3.6 Factores de Riesgo que Afectan a la Diátesis

3.6.1 Factores Neurobiológicos que Afectan a la Diátesis

Disminución de la Función Serotoninérgica. La mayoría de los estudios del ácido 5-hydroxiindolacético (5-HIAA) (metabolito de la serotonina) en líquido cefalorraquídeo (LCR) en depresión mayor con y sin conducta suicida han demostrado niveles menores en intentos de suicidio en comparación con pacientes sin intentos (Mann y Malone, 1997). Además, niveles bajos de 5HIAA en LCR pueden predecir la muerte por suicidio en pacientes con depresión mayor (Nordström y cols., 1995) e intentos de suicidio en pacientes con esquizofrenia (Cooper y cols., 1992).

Los niveles de 5-HIAA en LCR parecen estar genéticamente regulados (Mann y cols., 1999a), y la heredabilidad de la función serotoninérgica sugiere que este efecto es un marcador de rasgo más que de estado. Esto puede explicar por qué los niveles bajos de 5-HIAA en LCR se correlacionan con actos suicidas tanto pasados como futuros, ya sean cercanos o lejanos en el tiempo.

Los estudios postmortem de víctimas de suicidio en comparación con controles sanos y con controles con trastornos psiquiátricos muestran anomalías serotoninérgicas en el núcleo dorsal del rafe y en la corteza prefrontal (PFC) ventral (Mann y cols., 1999a). La unión al transportador de serotonina está reducida en la corteza prefrontal ventral y la unión al receptor 5-

HT1A parece estar incrementada en la misma área cerebral (Mann y cols., 1999a). Esto sugiere que la función serotoninérgica es menor en la corteza prefrontal ventral, lo cual produce un incremento compensador en los receptores serotoninérgicos postsinápticos. Así, la disminución de la función serotoninérgica ha sido implicada en la conducta suicida y es probable que se asocie con un umbral disminuido para ejecutar las ideas suicidas.

Agresividad/Impulsividad. Los pacientes con depresión mayor que realizan intentos de suicidio tienden a tener mayores niveles de agresividad e impulsividad que los que no lo intentan (Mann y cols., 1999b). Además, la conducta agresiva se ha relacionado con la disminución en la función serotoninérgica a través de cifras bajas de 5-HIAA en líquido cefalorraquídeo (Linnoila y cols., 1983), al igual que ocurre en la conducta suicida (Mann y Malone, 1997). En individuos impulsivos y agresivos, como los delincuentes violentos, aquellos con historia de intentos de suicidio presentaban niveles de 5-HIAA en líquido cefalorraquídeo más bajos que aquellos sin intentos de suicidio (Linnoila y Virkunen, 1992). De igual forma, los abusos físicos o sexuales durante la infancia se asocian con una tasa mayor de conducta suicida en el contexto de una depresión mayor (Mann y cols., 1999b), y aquéllos con historia de abuso también parecen ser más impulsivos y agresivos. Claramente, la disfunción serotoninérgica aparece implicada tanto en la agresividad como en el suicidio.

Es posible que tanto la agresión como la conducta suicida se relacionen con el mismo umbral bajo para actuar bajo poderosas pulsiones. Por lo tanto, posiblemente, las conductas agresivas y suicidas pueden compartir el mismo mecanismo de predisposición subyacente relacionado con la función serotoninérgica. Es también posible que los efectos ambientales tengan un impacto sobre ambos umbrales.

Colesterol. En la literatura se ha recogido la relación entre el colesterol bajo y la muerte accidental o por suicidio (Kaplan y cols., 1997). Se desconoce si esta asociación se debe a los efectos del colesterol sobre las tasas de depresión, el deterioro cognitivo o los niveles de agresividad. Se ha sugerido que la relación entre el colesterol bajo y la muerte por suicidio podría estar mediada por el efecto del colesterol sobre la función serotoninérgica.

3.6.2 Factores Psicobiológicos que Afectan a la Diátesis

Abuso Crónico de Sustancias. El suicidio consumado está a menudo asociado con el uso de sustancias, especialmente alcoholismo. En un estudio (Cornelius y cols., 1995) comparando pacientes con depresión mayor y dependencia alcohólica, y pacientes con uno solo de estos trastornos, los pacientes que tenían los dos

trastornos eran los que tenían una mayor ideación suicida frente a los que sólo eran alcohólicos, y los deprimidos sin abuso de alcohol se colocaban entre estos dos grupos. El mecanismo por el que el abuso crónico de sustancias incrementa el riesgo de suicidio se desconoce. Sin embargo, la depleción de serotonina producida por el abuso crónico de sustancias probablemente juega un papel en la disminución del umbral para actos suicidas.

Enfermedades Físicas Crónicas. Las enfermedades físicas crónicas se han asociado tradicionalmente con el suicidio. Sin embargo, entre las enfermedades crónicas, parece ser que las que afectan al sistema nervioso central están más relacionadas con el suicidio. Por ejemplo, los pacientes con esclerosis múltiple, enfermedad de Huntington, epilepsia e infección por VIH tienen tasas más altas de suicidio que otras enfermedades crónicas (Coté y cols., 1992). Cerca de la mitad de todos los pacientes con esclerosis múltiple sufren depresión durante el curso de la enfermedad (Stenager y cols., 1992), el 28% hacen tentativas de suicidio y el 46% presentan ideación suicida (Stenager y cols., 1996). El riesgo de suicidio de los pacientes con esclerosis múltiple es 1.83 veces superior al de la población general (Stenager y cols., 1992), y la mitad de los suicidios ocurren en los 5 primeros años tras el diagnóstico. El riesgo en la enfermedad de Huntington esta incrementado de 4 a 8 veces respecto a la población general (Lipe y cols., 1993; Schoenfeld y cols., 1984), en particular en los pacientes deprimidos y sin demencia (Kraus, 1975). El riesgo en pacientes con epilepsia institucionalizados es 5 veces superior al de la población general, y 25 veces en aquellos con epilepsia del lóbulo temporal. Esta relación de mayor suicidabilidad se mantiene a pesar de controlar en las comparaciones el grado de incapacidad producido por la enfermedad (Mendez y Doss, 1992). Así, las enfermedades crónicas, especialmente aquellas que afectan al sistema nervioso central, disminuyen el umbral para llevar a cabo las ideas suicidas.

Abuso Infantil. En una muestra universitaria, una historia de abuso sexual en la infancia predice el riesgo de sufrir una depresión, autoagresividad crónica (conductas de riesgo, tendencia a los accidentes), ideas e intentos de suicidio, ideas y actos autolesivos (automutilaciones y abuso de sustancias). Cuanto más joven es la persona cuando sufre el primer abuso, más intentos de suicidio cometerá (Boudewyn y Liem, 1995). Además, niños que experimentan castigo corporal en la adolescencia tienen un mayor riesgo de síntomas depresivos, ideación suicida, abuso de alcohol, y abuso físico a sus propios hijos y esposa posteriormente en su vida adulta (Straus y Kantor, 1994). Desde una perspectiva diferente,

un estudio revela que las víctimas de suicidios consumados en adolescentes tienen una probabilidad 6 veces mayor que los controles de haber sufrido abuso infantil (Deykin y cols., 1985). A la vista de estos datos, parece que tanto el abuso físico como sexual en la infancia incrementa la vulnerabilidad hacia la conducta suicida, incluyendo el suicidio consumado.

3.6.3 Factores Ambientales que Afectan a la Diátesis

Las redes sociales de las personas con intentos de suicidios son más débiles que las de las personas que no lo intentan. Los varones que fallecen por suicidio a menudo tienen una experiencia reciente de disputa familiar o pérdida del empleo (Heikkinen y cols., 1994). Las mujeres que se suicidan presentan más frecuentemente una enfermedad en la familia, la muerte de un familiar o un amigo cercano o una disputa familiar en comparación con mujeres fallecidas por otras causas.

El Soporte Social. El soporte social es un constructo complejo que puede ser concebido como un conglomerado de factores que incluyen relaciones matrimoniales, descendencia, familia extendida y relaciones laborales, entre otros.

Algunos estudios de conducta suicida en depresión mayor han encontrado problemas conyugales, tales como separación o divorcio entre los pacientes con mayor riesgo de suicidio (Malone y cols., 1995a). Por contra, la existencia de niños en el hogar parece proteger contra la conducta suicida, especialmente en mujeres (Hoyer y Lund, 1993) pero también en general (Malone y cols., 1995a; Hoyer y Lund, 1993; Axelsson y Lagerkvist-Briggs, 1992). La presencia de familia extendida puede proveer de un soporte social y ofrecer protección contra las ideas suicidas (Hope y Martin, 1986). Así, las relaciones con el cónyuge, familia extensa o hijos menores de 18 años viviendo en casa por quienes se siente responsabilidad, aumentan el umbral para el suicidio.

Creencias Religiosas y Otras Razones para Vivir.

Los individuos con intentos de suicidio perciben menos razones para vivir que aquellos que nunca han hecho un intento (Malone y cols., 1995a; Linehan y cols., 1983). Esto es así incluso cuando el intento de suicidio ocurre meses antes de la valoración de las razones para vivir. Por lo tanto, tener creencias morales, religiosas o familiares contra la conducta suicida puede proteger a los individuos vulnerables e incrementar el umbral para pasar al acto desde las ideas de suicidio.

3.7 Aproximaciones Terapéuticas

El tratamiento de la conducta suicida tiene dos aspectos fundamentales. Por un lado, la intervención directa sobre la propia conducta, que

requiere a menudo medidas de prevención que eviten el paso al acto, como puede ser la valoración de hospitalización. El segundo aspecto es el abordaje terapéutico de la patología y conflictos que modifican el umbral para la conducta suicida.

La elección del tratamiento dependerá del riesgo suicida, de la patología psiquiátrica presente, de las complicaciones médicas si las hubiere y de la actitud del paciente ante el plan terapéutico. Se puede establecer un contrato terapéutico de no suicidio. Este abordaje puede ser útil para descargar la tensión del terapeuta, e iniciar una discusión franca con el paciente sobre el suicidio y sus consecuencias. Es importante utilizar en un primer momento el alivio sintomático mediante ansiolíticos. Si se puede evitar el ingreso, se establecerá finalmente el calendario de visitas y un plan en caso de urgencia.

3.7.1 Evaluación del Riesgo Suicida

Los pacientes con ideación suicida que acuden al médico de cabecera deben remitirse a un psiquiatra. En caso de que la ideación haya dado lugar a un acto de autolesión deben ser remitidos a un hospital general para la evaluación de las consecuencias médicas y para realizar una valoración psiquiátrica.

Todos los pacientes atendidos en un hospital por conductas autolesivas deben ser valorados por un psiquiatra, de cara a identificar los motivos del acto así como trastornos mentales potencialmente tratables. Sólo deben ser dados de alta si han sido valorados y se ha fijado un plan de atención posterior. La intencionalidad de la conducta suicida es muy difícil de medir y a menudo los pacientes atendidos por conducta suicida se muestran muy ambivalentes. Al valorar una conducta suicida se deben fijar 3 objetivos: conocer la comorbilidad psiquiátrica tanto aguda como crónica, las circunstancias y motivaciones de la conducta, y evaluar los factores de riesgo de suicidio a corto plazo (a menudo ligado a psicopatología potencialmente tratable).

En la tabla 1 se resumen los datos necesarios para realizar la correcta valoración del intento de suicidio así como sugerencias para realizar la entrevista clínica.

Nicholas y Goleen (2001) proponen la hospitalización si existen intentos previos de alta letalidad, plan detallado, acceso a medios letales, pérdida reciente, aislamiento social, desesperanza, historia de conductas impulsivas y de alto riesgo, abuso de sustancias y trastorno mental sin tratamiento. Estos autores recomiendan considerar el tratamiento ambulatorio si no hay intentos previos de alta letalidad, no existe plan, la familia colabora y/o hay buen soporte social y no hay acceso a medios letales. Siempre hay que tener presente que es imposible predecir el riesgo individual de suicidio.

3.7.2 Psicoterapia de la Conducta Suicida

Existen datos prometedores sobre la eficacia de las terapias de tipo cognitivo-conductual aunque todavía sin resultados concluyentes en la prevención de recaídas y sin que haya quedado claro qué tratamientos son los más eficaces. Las técnicas de resolución de problemas parecen especialmente adecuadas. La terapia interpersonal psicodinámica breve puede resultar eficaz en tentativas suicidas pero se necesitan más estudios que lo demuestren.

3.7.3 Psicofarmacología de la Conducta Suicida

Aparte del uso de la clozapina en trastornos psicóticos (Meltzer et al 2002), no existe todavía un tratamiento específico para la suicidabilidad por lo que es fundamental tratar la patología psiquiátrica de base. El antidepresivo a elegir debe ser eficaz ante todo y seguro en sobredosis. Se suelen preferir antidepresivos de tipo sedante, pero si se elige un ISRS se puede asociar una benzodiacepina. Los casos de depresión delirante requieren antipsicóticos. También se debe añadir medicación sedante después de una tentativa con psicofármacos hasta la instauración del antidepresivo y al principio del tratamiento antidepresivo, por el conocido aumento del riesgo suicida. Si bien los antidepresivos juegan un papel muy relevante en la prevención del suicidio, no se les ha podido demostrar un efecto específico de prevención de la conducta suicida, a diferencia del litio cuya eficacia incluye tanto pacientes unipolares como bipolares. En cualquier caso no se debe supeditar la eficacia del tratamiento a la seguridad del mismo.

En la Esquizofrenia es preciso tratar de forma específica la sintomatología depresiva y evitar los efectos secundarios, especialmente la acatisia, manteniendo la eficacia antipsicótica. Existen reportes en la literatura de casos de suicidios posiblemente precipitados por acatisia. Los estudios con antipsicóticos atípicos no son todavía concluyentes y solo la clozapina parece tener efectos anti-suicidas (Meltzer et al 2002).

3.7.4 Terapia Electroconvulsiva

La terapia electroconvulsiva es para algunos autores el tratamiento de elección de los pacientes con trastornos afectivos con riesgo suicida agudo. Otros autores destacan su indicación en casos con índices de endogenidad. La revisión de la literatura coincide en un profundo efecto sobre la suicidabilidad a corto plazo con muy poca evidencia, en caso de haber alguna, de un efecto positivo a largo plazo, entre otras cosas por la dificultades en el mantenimiento de esta terapia.

3.7.5 Intervención en Crisis

Es prioritario identificar la crisis suicida. Los problemas de comunicación entre el paciente y el

Predictores clínicos de conducta suicida

terapeuta pueden interferir de forma importante en la identificación de la crisis. Es por ello que

acotar la relación terapéutica fijando límites claros es fundamental.

Tabla 1. Aspectos a valorar en pacientes con conductas relacionadas con el suicidio.

Aspecto a valorar	Preguntas
Factores sociodemográficos	Hombres, tercera edad, solteros, blancos, soledad y falta de red social
Estresantes	¿Como van las cosas con su familia / en el trabajo...? Salud, situación económica, laboral, legal, familiar y relación de pareja
Depresión, ansiedad o agitación	¿Ha notado/experimentado en las dos últimas semanas...? Dificultades para la concentración, insomnio, apetito, astenia, tristeza, anhedonia, desinterés, autoestima, inquietud, ansiedad, angustia, agitación, nerviosismo
Impulsividad	Rasgos de impulsividad y/o agresividad
Abuso de alcohol (CAGE) y drogas	¿Ha tenido alguna vez la sensación de que tenía que dejar de beber? ¿Le han criticado los demás por lo que bebe? ¿Ha tenido sentimientos de culpa por haber bebido? ¿Ha tenido que beber por la mañana para calmar sus nervios?
Factores fisiológicos	Intoxicación aguda Trastornos mentales orgánicos Enfermedades somáticas
Desesperanza	Pérdida de la principal razón para vivir del paciente Pérdida de la capacidad de afrontamiento Vulnerabilidad al sufrimiento (soledad, enfermedad...) Expectativas negativas
Ideación suicida	¿Ha tenido pensamientos sobre la muerte o el suicidio? Finalidad del suicidio (escapar, venganza, resolver problemas) Significado del suicidio para el paciente (renacer, reunirse) Planes/Impulsividad Medios disponibles, letalidad, violencia Ensayos preliminares ¿Puede resistir los impulsos? Voces que le inducen al suicidio
Antecedentes personales y familiares	Historia de autolesiones (¿en qué medida se tranquilizaba?) Intentos previos, intencionalidad, circunstancias (¿similares a lo actual?). Conducta suicida en la familia y círculo social
Autolesión	Letalidad y consecuencias médicas Aislamiento Arrepentimiento
Competencia y colaboración	Capacidad y competencia del paciente para participar en el tratamiento. Capacidad para desarrollar una alianza terapéutica

4 INTRODUCTION

Abstract

Suicidal behavior can be understood as the result of the interplay between an individual's threshold for acting on suicidal ideas and the presence of stressors or triggers for the suicidal act. Classifying risk factors as affecting the threshold for suicidal behavior or serving as triggers may clarify how they interact with each other and may ultimately provide insights regarding suicide prevention.

4.1 Definition of Suicidal Behavior

Suicidal behavior encompasses a spectrum. It includes completed suicide in which the person intentionally causes his or her own death; suicide attempt in which the person causes some injury to him or herself with the intent of ending their life; and suicidal ideation meaning that the person thinks about wishing to end their life. Even within these categories, a wide range of manifestations exists. For example a suicide attempt with intent to die may result in very little medical damage as is the case when the patient makes superficial cuts to the skin or takes an overdose of a substance that is low in toxicity. In contrast, severe attempts, also known as failed suicide, can have dire medical consequences and lead to significant morbidity as is the case when a patient survives jumping from a height but suffers multiple fractures. Suicidal ideation can also be of varying intensities. Some patients report fleeting thoughts about wishing they were dead whereas others may report a morbid preoccupation with methods to kill themselves. In this chapter we will discuss the epidemiology of suicidal behavior, its association with psychiatric conditions and describe a model for understanding risk for suicidal acts in psychiatric diagnoses in general.

4.2 Epidemiology of Suicidal Behavior

Suicide is a leading cause of death world-wide (La Vecchia y cols., 1994). Mortality varies across countries with Hungary and Sri Lanka reporting the highest rates (52.12 and 49.62/100,000, respectively) and Egypt reporting the lowest (0.08/100,000). Latin American countries and Spain all report levels below 15.5/100000. In addition, rates of suicide are generally higher in males than females, and suicide affects youth and the elderly disproportionately. Moreover, suicidal behavior appears to vary along ethnic or cultural lines. Rates of suicide attempt and suicidal ideation also vary across countries. One cross national study of 9 countries revealed that the highest rates of attempt and ideation were present in Puerto Rico whereas the lowest were in Beirut, Lebanon.

4.3 Association of Suicidal Behavior with Psychiatric Diagnoses

Psychological autopsy studies in which the suicide victim's psychiatric and psychological history is gathered after the death by interviewing family and physicians of the deceased, have shown that 90 to 95% of all suicide victims in Western countries have at least one diagnosable psychiatric condition. This figure is even more impressive when one considers the limitations of making a diagnosis without the benefit of interviewing the patient directly. The reasons why persons take their life are multiple. Yet, the presence of a psychiatric diagnosis is a critical factor in suicide completion.

The relationship of suicide to specific diagnoses has received significant attention. For example, studies estimate that in schizophrenia 10 to 15 percent of all patients die by their own hand. In contrast, studies of major depressive disorder, unipolar type have revealed that the suicide risk ranges from 2 percent to 15 percent. In outpatient subjects with major depression, the rate is estimated to be closer to 2 percent. The rate in groups with severe depression requiring hospitalization is closer to 15 percent. Perhaps the diagnosis with the highest rate of suicide is bipolar disorder. A meta-analysis of studies examining suicide in bipolar disorder has found that 15 to 20 percent of patients with bipolar disorder die by suicide. Similarly, rates of suicide in substance abuse are also high and in fact when substance abuse is comorbid with either schizophrenia, major depression or bipolar disorder the risk for suicide in these conditions increases substantially. Of note, patients with character pathology are also at risk for suicide. This is of critical importance in particular in borderline personality disorder, a disorder in which suicidal threats or behaviors are often viewed by clinicians as manipulative. Nonetheless, the rate of suicide in borderline personality disorder is estimated to be between 8 and 10 percent.

4.4 A Model for Understanding Suicidal Behavior: The Stress-Diathesis Model

The focus of studies has often been on precipitants of suicidal behavior or stressors. In the previous section we describe the importance of the presence of a psychiatric illness as a factor in suicidal behavior. However, it is also known that not all patients with psychiatric conditions attempt or complete suicide. In fact, the vast majority of patients with psychiatric illnesses do not attempt or complete suicide.

One way to understand the relationship between psychiatric conditions and suicide is to conceptualize the risk as being related to other underlying factors or characteristics of the patient that place that person at risk for acting on suicidal thoughts. The presence of a stressor such as the development of a major depressive episode, financial duress, disruption of important emotional relationships, or problems in one's employment or career determine the timing of the suicidal act. However, without the underlying diathesis or vulnerability to suicidal behavior, the suicidal act will not occur.

Factors that are related to this underlying vulnerability towards suicidal behavior have been postulated to include a tendency to aggression or impulsivity. The diathesis may also be related to genetic or heritable factors since suicide appears to run in families separate from the inheritance of psychiatric conditions. In addition, a propensity for pessimism, or for experiencing symptoms more acutely despite no difference in objective severity of symptoms may be a factor in suicidal behavior, as well. We know also that psychosocial factors such as a history of childhood physical or sexual abuse may also predispose patients towards suicidal behavior.

Whether these factors, which contribute to a diathesis or vulnerability for acting on suicidal thoughts are related to serotonergic deficits has been the object of many studies. It is well known that low serotonergic functioning is associated with suicidal acts, especially with suicidal acts that are of high lethality or serious medical consequences.

Risk factors that are associated with suicidal behavior come from a variety of domains. Some appear to be related to genetics or other heritable factors (Mann y cols., 1999a). However, as mentioned above, suicide appears to run in families independent of other heritable psychopathological conditions such as affective disorders, schizophrenia or alcohol abuse (Brent y cols., 1996; Egeland y Sussex, 1985). Other risk factors appear to be related to environmental effects, such as rearing, the availability of lethal methods or the disruption of important emotional relationships. We have proposed a comprehensive

model (Mann y cols., 1999b) which categorizes risk factors into two domains. In this model, suicide is an outcome that requires both a stressor and a diathesis. As such, there must be a precipitant or trigger for suicidal behavior to occur, yet the person must also have a diathesis or vulnerability towards acting on suicidal thoughts. Risk factors associated with suicide are categorized as either affecting the diathesis or threshold for acting on suicidal ideation or acting as stressors or precipitants.

4.5 Risk Factors Acting as Stressors or Precipitants

Precipitating risk factors may be biological, psychological or environmental in nature. Because it is often difficult to clearly categorize an internal stressor as biological or psychological, we combine them as psychobiological in contrast to environmental in nature.

4.5.1 Psychobiological Stressors

Episodes of Psychiatric Illness. The presence of an acute psychiatric episode such as depression or psychosis is not a sufficient condition for suicide, because although 10-20% of patients with major psychiatric disorders such as bipolar or unipolar affective illness or schizophrenia die by suicide (Mann y cols., 1999b), most patients with these conditions never attempt suicide. Yet, completed suicide occurs rarely outside the context of a psychiatric illness, as previously noted. About 90% of all suicides have a psychiatric disorder (Mann y cols., 1999b). Approximately 60% of all completed suicides occur when the person is in a Major Depression (Barraclough y cols., 1974; Isacson y cols., 1992). Thus, the presence of a psychiatric illness may be thought of as a necessary, but not sufficient requirement or stress for the occurrence of suicide.

Acute Substance Intoxication. Acute intoxication often plays a role in completed suicide. It can be both a "tool" utilized by the suicide victim to facilitate the act or the intoxication can play a disinhibiting role, causing the person to act on suicidal ideas that they would otherwise ignore. The role often cannot be elucidated. About 60% of youth take a sedative or alcohol in the context of a suicide attempt. In addition, acute intoxication has important neurobiological effects which may have direct consequences for suicidal behavior, including an acute surge in serotonergic and dopaminergic release, followed by a relative depletion (Mann y cols., 1999a). As such, acute intoxication may be a trigger with a complex relationship to suicidal behavior with either facilitating or causal effects.

4.5.2 Environmental Stressors

Contagion. Especially among youth, contagion or imitation has often been posited as causal when clusters of suicides occur (Schmidtke y Häfner, 1988). The occurrence of an adolescent suicide in

the community may facilitate the behavior in vulnerable individuals in the community such as those who are depressed or abuse substances. In addition, the recent publicity given to the use of assisted suicide may also increase the rate of completed suicide among the elderly or infirm. Furthermore, assisted suicide and euthanasia are likely to contribute to an underestimation of suicide rates (Diekstra, 1993). In these ways, contagion may serve as a trigger for suicidal behavior.

Family, Financial or Social Crisis. Family discord and difficulties at work have been reported to be risk factors for completed suicide in both men and women (Heikkinen y cols., 1994). For males, the presence of financial problems may also increase the risk for suicidal acts. Females also appear to be at higher risk if they have recently experienced the death of a relative or close friend. These types of losses or crises then appear to serve as stressors that precipitate suicidal behavior. However, because these types of crises are common stressors but also may be consequences of psychiatric disorders, their additional importance in triggering suicide is difficult to estimate.

4.6 Risk Factors Affecting the Diathesis

4.6.1 Neurobiological Factors Affecting the Diathesis

Low Serotonergic Functioning. Most studies of cerebrospinal fluid (CSF) levels of the serotonin metabolite- 5-hydroxyindoleacetic acid (5-HIAA) in major depressives with and without suicidal behavior have demonstrated lower levels in suicide attempters compared to nonattempters (Mann y Malone, 1997). In addition, low levels of CSF 5HIAA may predict eventual death by suicide in patients with Major Depression (Nordström y cols., 1995) and suicide attempts in patients with Schizophrenia (Cooper y cols., 1992).

CSF 5 HIAA appears to be under significant genetic regulation (Mann y cols., 1999a) and the heritability of serotonin functioning suggests that its effects are trait rather than state related. That may explain why low CSF 5-HIAA correlates with past and future suicidal acts regardless of how recent or remote.

Postmortem studies of suicide victims have shown that compared to normal controls and to psychiatric controls, suicides have serotonergic abnormalities in the dorsal raphe nucleus and in the ventral prefrontal cortex (PFC) (Mann y cols., 1999a). Serotonin transporter binding appears to be reduced in the ventral PFC and 5HT1A receptor binding appears to be increased in this same brain area (Mann y cols., 1999a). This suggests that there is less serotonergic functioning in ventral cortex, leading to a compensatory

increase in post-synaptic serotonin receptors. Thus, lower serotonergic functioning has been implicated in suicidal behavior and is likely to be associated with a lower threshold for acting on suicidal ideas.

Aggression/Impulsivity. We and others have found that in patients with Major Depression, those who are suicide attempters tend to have higher levels of aggression and impulsivity than nonattempters (Mann y cols., 1999b). In addition, aggressive behavior and suicidal acts are reportedly related to lower serotonergic functioning as shown by lower CSF 5-HIAA (Linnoila y cols., 1983), as is suicidal behavior (Mann y Malone, 1997). In impulsive, aggressive individuals, such as violent offenders, those with a history of suicide attempts have lower CSF 5HIAA than those without suicide attempts (Linnoila y Virkunen, 1992). Furthermore, we have reported that physical or sexual abuse during childhood is associated with a higher rate of suicidal behavior in the context of Major Depression (Mann y cols., 1999b) and those with abuse histories also appear to be more impulsive and aggressive. Clearly, serotonergic dysfunction appears to be implicated in both aggression and suicide. It is possible that both aggression and suicidal behavior are related to the same lower threshold for acting on powerful feelings or urges. And therefore, both suicidal and aggressive behavior may share an underlying predisposing mechanism related to reduced serotonergic functioning. It is also possible that environmental effects have an impact on both aggression and suicide threshold.

Cholesterol. The relationship between naturally low and clinically reduced cholesterol and nonillness death by suicide or accidents has recently been noted in the literature (Kaplan y cols., 1997). Cross sectional population studies have demonstrated this association. Studies of nonhuman primates have shown that monkeys on low cholesterol diets have a blunted prolactin response to fenfluramine and lower CSF 5-HIAA. Whether this association is due to the effects of cholesterol on rates of depression, impaired cognitive functioning or individual levels of aggression is unknown. However, the association between suicide and low cholesterol is likely to be mediated through lowered serotonergic function, which in turn contributes to the diathesis for acting on suicidal thoughts.

4.6.2 Psychobiological Factors Affecting the Diathesis

Chronic Substance Abuse. Completed suicide is often associated with substance abuse, especially alcoholism. In a study (Cornelius y cols., 1995) comparing patients with Major Depression and Alcohol Dependence, Major Depression alone and Alcohol Dependence alone, depressed

subjects who had comorbid Alcohol Dependence had a higher level of suicidal ideation compared to depressed subjects without Alcohol Dependence. The patients with Alcohol Dependence alone had the lowest levels of suicidality. How chronic substance abuse increases the risk for suicide is unknown. However, the serotonin depleting consequences of chronic substance abuse are likely to play a role in lowering the threshold for suicidal acts.

Chronic Physical Illnesses. Chronic physical illness has long been associated with suicide. However, among chronic illnesses, it appears that those affecting the central nervous system are more likely to lead to suicide. For example, patients with Multiple Sclerosis, Huntington's Disease (HD), seizure disorders and Acquired Immune Deficiency Syndrome (Coté y cols., 1992) have higher rates of completed suicide when compared to other chronic illnesses. Close to half of all patients with multiple sclerosis have been found to suffer from depression during the course of their illness (Stenager y cols., 1992), 28% made suicide attempts and 46% had suicidal ideation (Stenager y cols., 1996). Multiple sclerosis patients were 1.83 times more likely to die from suicide than the general population (Stenager y cols., 1992) with half of the suicides occurring in the first 5 years after diagnosis. The risk of suicide in HD is increased 4 to 8 times over general population (Lipe y cols., 1993; Schoenfeld y cols., 1984). In particular, patients who are depressed but not demented are at highest risk (Kraus, 1975). The risk for suicide is fivefold in institutionalized patients with epilepsy and 25 times in those suffering from temporal lobe epilepsy. When degree of disability is controlled for, epileptics still have a higher rate of suicide than those with other disabilities (Mendez y Doss, 1992). Thus, chronic illnesses, especially those affecting the CNS appear to decrease the threshold for acting on suicidal ideas.

Child Abuse In a sample of college students, a history of sexual abuse in childhood predicted depression, chronic self-destructiveness such as risk taking and accident proneness, suicide ideation and attempts, self harm ideation and acts (self-mutilation and substance abuse). The younger the age of the person when first abused, the more suicide attempts s/he reported (Boudewyn y Liem, 1995). In addition, children who experienced corporal punishment in adolescence had a greater risk of depressive symptoms, suicidal ideation, alcohol abuse, and in turn physical abuse of their own children and wife later in life. Suicidal ideation increased markedly with the frequency of adolescent corporal punishment for both men and women (Straus y Kantor, 1994). From a different perspective, a study of completed adolescent suicides revealed

that adolescent suicides were six times more likely than controls to have been victims of child abuse (Deykin y cols., 1985). As such, it appears that both childhood physical and sexual abuse increase the vulnerability towards suicidal behavior, including but not limited to completed suicide.

4.6.3 Environmental Factors Affecting the Diathesis

Social networks amongst attempters have been reported to be weaker than among nonattempters. In a series of suicides (Heikkinen y cols., 1994), males often had recently experienced family discord and unemployment. Women who suicided more often had recently had an illness in the family, the death of a relative or close friend or family discord compared to women with other causes of death.

Social Support. Social support is a complex construct that can be thought of as having components that include marital relationships, offspring, extended family and work relationships, among other things.

Some studies of suicidal behavior in Major Depression have found that a disrupted marital status, such as being separated or divorced placed patients at higher risk (Malone y cols., 1995a). In contrast, having children under the age of 18 living in the home appears to be protective against suicidal behavior, especially for women (Hoyer y Lund, 1993) but also in general (Malone y cols., 1995a; Hoyer y Lund, 1993; Axelsson y Lagerkvist-Briggs, 1992). The presence of extended family may also provide social support and offer protection against acting on suicidal thoughts. Hoppe and Martin (Hope y Martin, 1986) offer the concept of familism as an explanation for the finding that Mexican Americans have lower rates of completed suicide than the general population in the United States. Familism, or an emphasis on close relationships with extended kinship, may offer protection against stress and serve as a protective factor against suicide. Thus, relationships with a spouse, extended family or offspring under the age of 18 living at home for whom the person feels responsible may increase the threshold for suicide.

Religious Beliefs and Other Reasons for Living. We (Malone y cols., 1995a) and others (Linehan y cols., 1983) have shown that suicide attempters give fewer reasons for living than those who have never made an attempt. This is so even when the suicide attempt occurred months before the assessment of reasons for living. Thus, having moral, religious or familial constraints against suicidal behavior may protect otherwise vulnerable individuals and raise their threshold for acting on suicidal ideas.

5 RESEARCH ON SUICIDAL BEHAVIOR. STATE OF THE ART

Abstract

Retrospective and cross-sectional studies can identify correlations between clinical and other factors and suicidal behavior, but can neither test predictive utility nor ascertain causal relationships. Prospective studies are better able to examine the predictive power of such correlations (Kraemer y cols., 1994).

Future studies must be comprehensive to assess putative risk factors and examine their relative importance in predicting risk. Such studies will permit development and refinement of predictive models that use multiple domains, and which may assist clinicians in identifying patients at risk.

5.1 Intervention Research for Suicidal Behavior

The Declaration of Helsinki states that: “The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.” Nowhere is the lack of proven therapeutic methods greater than in the prevention of suicidal behavior. Since suicide is the third leading cause of death in those under age 44 (WHO, 2002), the lack of randomised controlled trials that examine suicide prevention is remarkable.

Reasons for such a dearth of intervention research include: a propensity for conceptualising suicidal behavior as a general symptom of psychiatric conditions, such as schizophrenia, rather than as a specifically targetable outcome; medicolegal concerns about doing research with individuals who exhibit self-destructive behaviors (NIMH, 2001); and the ethical and scientific challenges of maintaining safety for participants in such studies (Pearson y cols., 2001). The ethical dilemmas of the best design are thorny, including those posed by the use of placebo to minimise the occurrence of type II statistical errors arising from failed trials of efficacy rather than using treatment-as-usual interventions as comparators that putatively expose subjects to less risk.

One strategy to circumvent these problems is to examine the effects of therapeutic interventions on suicidal behavior in analysis or meta-analyses of data developed to assess the general efficacy of pharmacotherapy on conditions such as major affective disorders or psychotic disorders. This approach compensates for the low base rate of suicidal acts, because a large number of patients are included. Indeed most controlled studies reporting pharmacological effects on suicidal behavior have used this approach (Montgomery y cols., 1995; Rouillon y cols., 1989; Filteau y cols., 1993; Thies-Flehtner y cols., 1996; Khan y cols., 2000).

Using a meta-analytic approach, Jitschak Storosum and colleagues (2003) recently examined suicide attempts and completions in participants in randomised trials of atypical antipsychotics submitted to the Medical Evaluation Board in the Netherlands for approval of an indication in schizophrenia. These investigators surveyed 31 studies done between 1992 and 2002 involving 7,152 patients, 1,888 of whom were on placebo. At least 3,759 participants were enrolled in studies that explicitly excluded suicidal patients.

There was no difference in the rates of suicidal acts in those on active drug compared with those on placebo.

5.2 Period of Highest Risk

Prospective studies suggest that the period immediately following discharge from hospital is the time of highest risk. Follow-up studies have reported that the 6- to 12-month period immediately following hospitalization carries the highest risk of both suicide completion and attempt for those with depressive disorders (Fawcett y cols., 1990; Oquendo y cols., 2002; Gladstone y cols., 2001; Schneider y cols., 2001) with the first 2 months carrying the highest risk (Oquendo y cols., 2004b). However, risk of suicidal behavior remains elevated. Brodaty et al. (1997) reported that 38% of suicides occurred within 2 years of index admission, and 61% after 5 years, and Angst et al. (2002) document a persistent risk of suicide over 25 years of follow-up.

5.3 Risk Factors for Suicidal Behavior

5.3.1 Past Suicidal Behavior

A history of attempted suicide has consistently been documented to increase risk of eventual suicide completion. A 1967 meta-analysis of 15 prospective studies documented a 10–20% increase in the risk of completion among previous attempters (Dorpat y Ripley, 1967) and subsequent prospective studies have reported that a history of attempting suicide significantly increases the risk of future completion in depressed individuals (Fawcett y cols., 1990;

Schneider y cols., 2001; Angst y cols., 2001). No studies assessing the impact of a past suicide attempt on the risk of suicide conclude otherwise. Prospective studies reporting on repeat suicide attempters concur that a history of previous attempts increases the risk of a future non-fatal attempt (Fawcett y cols., 1990; Oquendo y cols., 2002; Oquendo y cols., 2004b; Paykel y Dienelt, 1971; Sokero y cols., 2005; Harrington y cols., 1990; Duggan y cols., 1991; Zweig y Hinrichsen, 1993). Moreover, repeated suicide attempts compound risk, with each repeat attempt incrementally affecting the risk of future attempts (Leon y cols., 1999). Leon y cols. (1999) calculated that for each prior attempt, the risk of a subsequent suicide attempt increased by approximately 32%. We replicated this result in a different sample finding a 30% increase in the risk of completion or a further attempt for each previous attempt that the individual has made (Oquendo y cols., 2002).

Of interest, one 10-year follow-up study reported that subjects who completed suicide had significantly fewer past attempts than surviving attempters (Gladstone y cols., 2001). This is consistent with the understanding that suicide completers and attempters are distinct, although overlapping, cohorts, and that high-lethality suicide attempts are less common. Thus, a history of prior attempts may have a different predictive capacity for low-lethality suicide attempts vs. high-lethality attempts or completions.

5.3.2 Suicidal Ideation

Whether suicidal ideation is predictive of future suicidal acts is unclear. Three prospective studies found that suicide ideation predicted completed eventual suicide (Fawcett y cols., 1990; Schneider y cols., 2001; Angst y cols., 2001). In contrast, a 10-year follow-up study found that suicidal ideation did not predict eventual suicide, but was higher in those who had a history of prior suicide attempts at baseline but who did not complete suicide during follow-up (Gladstone y cols., 2001). In our analysis, we did not find that suicidal ideation alone predicted future suicide attempt or completion (Oquendo y cols., 2004b). Rather, it was most useful when integrated into a factor together with measures of subjective depression, reasons for living, and hopelessness. Together, these findings suggest that suicidal ideation is less useful as an independent predictor of suicidal behavior and may be best considered together with other risk factors such as impulsivity and aggression, or protective factors such as reasons for living.

5.3.3 Psychopathology

Some non-prospective studies have documented the higher risk of suicidal behavior conferred by a

diagnosis of bipolar disorder compared with other psychiatric illnesses (Chen y Dilsaver, 1996; Jamison, 1986; Goodwin y Jamison, 1990). However, Angst et al. (2002) found a significantly higher standardized mortality rate for suicide in Major Depressive Disorder (MDD) compared with bipolar disorder (26.7 vs. 12.3). In a prospective study of bipolar patients, type of bipolar episode at index did not differentiate those who attempted suicide from non-attempters over the course of a 5-year follow-up (Strober y cols., 1995). It has been suggested that suicide risk may increase during periods of rapid changes of depressive state, occurring mainly at the beginning and end of episodes (Angst y cols., 2002), and bipolar patients, especially those with rapid cycling, may be at a higher risk of such periods. In support of this notion, Coryell et al. (2003) found that rapid cycling bipolar patients had a higher risk of suicide attempts, but not completion, during follow-up than non-rapid cycling bipolar patients. The inconsistency regarding suicide risk in bipolar disorder and MDD may be due to the clinical difficulty of making a bipolar II or not otherwise specified (NOS) diagnosis given the propensity for under-reporting of hypomania.

We recently reported that melancholia increases risk of suicidal acts independently of depression severity (Grunebaum y cols., 2004). Prospective studies found no difference in suicide completions (Brodaty y cols., 1997; Lehmann y cols., 1988) or suicide attempts (Lehmann y cols., 1988), between endogenous and neurotic depression groups. A multicenter 10-year study found that the psychogenetic (neurotic, reactive, and exhaustion) depression group was more likely than the endogenous group to attempt suicide, but no more likely to complete (Thornicroft y Sartorius, 1993). In contrast, Duggan et al. (1991) reported that depressive subtype did not differentiate suicide attempters from nonattempters, but severe dysphoria and psychomotor retardation were related to subsequent suicide attempts. Thus, the role of specific psychopathological features of depressive episodes in predicting risk of suicidal behavior warrants further study.

Few prospective studies of suicidal behavior have examined the predictive value of psychosis in the context of major depression, and many prospective studies exclude psychotic patients. One study found suicide completers more likely to have hypochondriacal preoccupations or delusions, but not delusions of guilt or sin, compared with nonsuicides (Schneider y cols., 2001). Those with psychotic depression were twice as likely to reattempt in the 2-year follow-up as those with no psychosis (Warman y cols., 2004). Thus, whether psychosis in the context of

mood disorders is a predictor in suicidal behavior remains to be confirmed.

Recurrence or failure to achieve remission of mood episode increases risk of both suicide attempts and completions. Leon et al. (1999) reported that 72% of the 58 subjects who made further suicide attempts, or completed suicide, during follow-up did so while in an affective episode. Risk of suicide attempt during follow-up has been associated with a lack of remission of index episode (Paykel y Dienelt 1971). Compared with patients who achieve remission, there is a two-fold increase in the risk of suicide attempt in those achieving partial remission, and a seven-fold increase during a depressive episode (Sokero y cols., 2005). We found that relapse or recurrence of major depression increased the risk of suicide attempt seven-fold in the 2 years after discharge from hospital (Oquendo y cols., 2002), and others report that those experiencing recurrent episodes of depression are more likely to attempt suicide (Zweig y Hinrichsen, 1993; Haw y cols., 2003). In a study of older adults, only 18.2% of attempters experienced no relapse in the 1-year follow-up compared with 60.9% of non-attempters (Zweig y Hinrichsen, 1993). Further, the majority of attempters (81.8%) had no remission of the index MDD episode suggesting that those suffering treatment-refractory depression have an increased risk of suicide. Of note, we found that most depressed patients at the time of suicide attempt are untreated or on inadequate pharmacotherapy (Oquendo y cols., 2002).

5.3.4 Psychiatric Comorbidity

Cluster B Personality Disorders. Cluster B personality disorders in general (Sabo y cols., 1995), and borderline personality disorder (BPD) (Antikainen y cols., 1995; Mehlum y cols., 1994) in particular, elevate risk of suicidal behavior. Although a wealth of retrospective and cross-sectional studies have shown that comorbid cluster B personality disorder and Major Depressive Episode (MDE) is associated with increased suicidal behavior, only two prospective studies address this question. McGlashan compared suicidal behavior in patients with MDE alone, MDE with comorbid BPD, and BPD without a history of MDE. The comorbid MDE/BPD group had a significantly higher risk of suicide than BPD alone, and had twice the risk of suicide than MDE alone; however, this was not statistically significant (McGlashan, 1987). In contrast, no association is reported between DSM-III personality disorder diagnosis and suicidal behavior in an MDD sample followed for 18 years (Duggan y cols., 1991).

Given the paucity of prospective studies in this area and the consistent reports in cross-sectional studies that personality disorders are associated

with increased risk of suicidal behavior, the effect of comorbid personality disorders on suicide risk clearly warrants further research.

Cigarette Smoking and Alcohol and Substance Use Disorders. Alcohol use disorder has been associated in prospective studies with an increased risk of future suicidal behavior in those with depressive disorders (Maser y cols., 2002). Substance and alcohol use disorders may increase risk of suicidal behavior either through pharmacologically induced disinhibition, depletion of monoamines, or because of a common diathesis or relevant psychopathology such as aggression/impulsivity.

There are a few prospective studies in MDD samples that report on smoking and suicidal behavior. We found that cigarette smoking was predictive of suicidal behavior over the course of a 2-year follow-up of MDD and bipolar disorder patients (Oquendo y cols., 2004b). Epidemiological and cross-sectional studies have consistently found an association between smoking and completed suicide (Hemenway y cols., 1993; Miller y cols., 2000) and suicide ideation and attempt (Tanskanen y cols., 1998). However, the inability of such studies to establish associations as causal, limits their interpretation (Meulemans y cols., 1992; Phillips, 1992).

Perhaps some of the predictive power of this variable stems from its association with other risk factors such as aggression or substance abuse rather than from pro-aggressive effects of the dopamine release induced by cigarette smoking. We have shown that depressed cigarette smokers have lower serotonergic functioning than depressed non-smokers (Malone y cols., 2003) and depressed smokers are reported to have more aggressive impulsive traits (Angst y Clayton, 1998). Angst and Clayton have suggested that cigarette smokers may be more likely to suffer from MDE, antisocial personality disorder and BPD (Angst y Clayton, 1998). More prospective data regarding the association between cigarette smoking and suicidal acts would be useful in determining whether smoking precedes the mood disorder and suicidal behavior.

Traumatic brain injury. One prospective study found a history of traumatic brain injury (TBI) associated with increased likelihood of making a suicide attempt (Duggan y cols., 1991) and another did not (Oquendo y cols., 2004a). However, whether this is due to depression in these subjects or the presence of higher levels of aggression rather than the TBI per se requires further study. Even mild TBI appears to enhance aggressive traits and is more likely in individuals who were more aggressive prior to their injury (Oquendo y cols., 2004a).

Given the risk of suicidal behavior associated with head injury, antecedent impulsivity and the

impact of TBI on such traits through disinhibition, as well as the role of alcoholism and substance use disorders in TBI warrant further investigation.

5.3.5 Traits

Aggression and Hostility. Aggression and the prediction of suicidal acts have been examined in only one prospective study in a mood disorder sample.

We found that aggression scores alone did not predict suicidal behavior; however, when combined into an aggressive/impulsive factor they did predict suicidal acts on follow-up (Oquendo y cols., 2004b). In cross-sectional studies greater aggression/impulsivity has been associated with suicide attempts in MDD patients with comorbid cluster B personality disorders (Corbitt y cols., 1996; Malone y cols., 1995a) and we have reported a higher level of aggression, but not impulsivity, amongst suicide attempters in a sample of bipolar disorder (Oquendo y cols., 2000).

Additionally, impulsivity and aggression have been associated with suicide attempts in a sample of violent offenders with varied psychiatric diagnoses (Linnoila y cols., 1983). Thus, aggression is likely to be an important variable in the prediction of suicidal behavior, and may reflect a deficit in the capacity for restraint, consistent with observations of altered serotonin binding indices in ventral prefrontal cortex (Stanley y Mann, 1983), a brain region involved in behavioral inhibition.

Impulsivity. Two prospective studies have examined the role of impulsivity in suicidal behavior. A 14-year study of 995 predominantly MDD patients found impulsivity clustered with alcohol and substance abuse, past attempts, and other factors, associated with both long- (2–14 years after index) and short-term (within 1 year of index) suicide completion (Maser y cols., 2002). Interestingly short-term attempters did not have high impulsivity, although long-term attempters did. We did not find impulsivity alone predictive of suicidal behavior over the course of a 2-year follow-up in MDD and bipolar disorder; however, when combined with aggression into a factor it was predictive (Oquendo y cols., 2004b). The inconsistency between studies may be due to differences in the assessment of impulsivity and in sampling strategy.

In cross-sectional studies, impulsivity is associated with a history of suicide attempt in psychiatric patients (Apter y cols., 1993) and adolescents (Horesh y cols., 1999). We have reported that suicide attempters who require medical hospitalization for treatment of the sequelae of their attempt are less impulsive than attempters with less lethal behavior (Oquendo y cols., 2003a). Impulsivity appears related to the probability of a suicide attempt and inversely

related to the medical lethality of the attempt. Perhaps impulsivity diminishes the planning required to inflict more severe medical damage (Baca-Garcia y cols., 2001).

5.3.6 Other Clinical Variables

Hopelessness. There are mixed reports on the predictive value of hopelessness. Prospective studies have reported hopelessness to be associated with suicide attempts in the short term (12–18 months) (Maser y cols., 2002; Keller y Wolfersdorf, 1993; Sidley y cols., 1999), and with suicide in the longer term (Fawcett y cols., 1990; Schneider y cols., 2001). However, another study reports no association with eventual suicide amongst suicide attempters (Samuelsson y cols., 2006). An analysis of the interaction between suicide risk factors in the NIMH Collaborative Depression Study cohort found hopelessness to be significantly associated with suicidal behavior only in subjects without alcohol or substance abuse disorders (Young y cols., 1994). We found that when hopelessness was integrated into a pessimism factor, which also included other measures of subjective depression, suicidal ideation and reasons for living, it predicted suicidal behavior over a 2-year follow-up (Oquendo y cols., 2004b). Clearly this risk factor has a relationship to other predictors, and those other risk factors or a composite factor may be a better predictor of future suicidal behavior.

To conclude, prospective studies over the past 30 years have identified an array of predictive indicators for future suicidal acts. However, the data for many of these risk factors either derives from one study or is contradictory. We did, however, find several risk factors that appear to be robust. A history of past suicidal behavior, recurrent or refractory depression, alcoholism comorbid with major mood disorders all appear to increase risk.

Other putative risk factors, such as comorbidity with anxiety or eating disorders, stressful life events, imitation effects, as well as protective factors that may be of more immediate use in assessing risk in clinical settings have yet to be adequately addressed in prospective studies. Moreover, in designing prospective studies of suicidal behavior, methodological issues must be considered including the classification of suicidal behavior. For unambiguous attempts and suicide, this is not an issue, but for ideation and intent, and self-harm without the intention to die, the use of different rating instruments and methods may result in contradictory findings.

6 OBJETIVES AND HYPOTHESES

Abstract

Putative risk factors for suicide behavior will be evaluated for their ability to predict suicidal acts in a 2-year follow-up period. We also will examine the predictive effect of individual risk factors that we have hypothesized.

6.1 OBJECTIVES

We propose a stress-diathesis model of suicidal behavior based on retrospective studies of mood, psychotic, and personality disorders (Mann y cols., 1999b; Malone y cols., 1995a). In this model, stressors are observable precipitants for suicidal acts, including a depressive episode or life events such as financial difficulties or disruption of a relationship. The diathesis is characterized by a tendency toward pessimism and a propensity for aggression/impulsivity. Compared with nonpessimistic subjects, pessimistic subjects would tend to experience more severe suicidal ideation, to have higher subjective ratings of the severity of depression and hopelessness, and to perceive fewer reasons for living in response to an illness of comparable objective severity or to social adversity.

Aggression/impulsivity may be manifested as a history of aggressive or impulsive behaviors and the presence of comorbid cluster B personality disorders. Key indicators of the presence of the diathesis would be a personal history of suicide attempt, an indication that the patient had the propensity to act on suicidal impulses in the past, and a family history of suicidal behavior, given the documented heritability of both suicidality and mood disorders (Brent y cols., 2002, 2004).

To test if the presence of the diathesis predicted suicidal behavior in major depression, hypothetical risk factors for suicidal acts assessed at the time of study entry were identified on the basis of their correlation with past suicide attempts.

These factors were then evaluated for their ability to predict suicidal acts in a 2-year follow-up period. We also examined the predictive effect of individual risk factors that we determined were associated with a history of suicidal acts. We hypothesized that the presence of pessimism during an acute major depressive episode but not the objective severity of depression, as well as lifelong aggressive/impulsive traits, would predict future suicidal behavior. We also studied predictors to identify potential differences in their importance among men versus women, since the occurrence of suicidal behavior shows strong sex effects.

In addition to studying baseline predictors of suicidal behavior, we examined the effects of

factors that could influence suicide risk during the 2 year follow up period, namely, adequacy of antidepressant treatment that might mitigate suicide risk and occurrence of life events that might precipitate suicidal acts.

We focused on subjects who presented with major depressive episodes, because this group has the highest risk for suicidal acts (Dilsaver y cols., 1997). This approach may distinguish clinical characteristics that can be used at the time of presentation for treatment of a major depressive episode to identify patients at high risk for suicidal behavior.

6.2 HYPOTHESES

We focus on four aspects of suicidal behavior using a prospective approach.

6.2.1 Clinical Predictors of Suicidal Acts After a Major Depressive Episode in Affective Disordered Patients

To test if the presence of the diathesis predicted suicidal behavior in major depression, hypothetical risk factors for suicidal acts assessed at the time of study entry were identified on the basis of their correlation with past suicide attempts.

These factors were then evaluated for their ability to predict suicidal acts in a 2-year follow-up period. We also examined the predictive effect of individual risk factors that we determined were associated with a history of suicidal acts. We hypothesized that the presence of pessimism during an acute major depressive episode but not the objective severity of depression, as well as lifelong aggressive/impulsive traits, would predict future suicidal behavior.

6.2.2 Sex Differences in Clinical Predictors of Suicidal Acts After a Major Depressive Episode in Affective Disordered Patients

Across diagnoses, suicide attempters are typically women (Mann y cols., 1999b). To investigate potential contributors to differences in rates and types of suicidal behavior in the two sexes, we examined the predictive power of putative risk factors for suicidal acts identified in our previous cross-sectional (Mann y cols., 1999b) and prospective (Oquendo y cols., 2004b) studies, hoping to identify clinical characteristics for men and women at high risk for suicidal acts at the time they sought treatment for a major depressive

episode. We hypothesized that, apart from a history of attempted suicide, variables predicting suicidal acts would differ between the sexes. We postulated that aggression, hostility, and a history of substance use disorders would predict future suicidal behavior in men, while depressive symptoms, a history of childhood abuse, fewer reasons for living, and comorbid borderline personality disorder would do so in women.

6.2.3 Adequacy of Antidepressant Treatment

We prospectively studied the adequacy of antidepressant treatment for patients with and without a history of suicide attempts and its impact on suicidal acts in the 2 years after hospitalization for treatment of an episode of major depression. Antidepressant treatment was naturalistically delivered by physicians in the community. We predicted that patients who received more intensive antidepressant treatment or had less time in a major depressive episode after discharge from the hospital would be at lower risk for suicidal acts during the follow-up period.

6.2.4 Role of Life Events in Precipitating Suicidal Behavior

In order to examine the role of life events and the diathesis on the risk of suicidal behavior, we conducted a prospective study of individuals with Major Depression. We followed depressed patients prospectively for 2 years as they received treatment as usual in the community. During the follow-up period, we assessed individuals for the occurrence of suicidal behavior, monitored the course of their depressive illness, and documented stressful life events. We have previously noted that the presence of a diathesis for suicidal behavior characterized by either pessimism or aggression/impulsivity increased the risk of suicidal behavior during the follow-up period (Oquendo y cols., 2004b). We now take the next step in testing our hypothesis and postulate that suicidal behavior will be more common in those with the diathesis for suicidal acts in the setting of either a major depressive episode or a life event.

7 MATERIAL Y MÉTODOS

Abstract

Research on suicidal behavior raises several ethical issues and must strictly follow ethical guidelines. All participating patients signed informed consent forms which fulfilled the three requirements of informed consent (information, voluntariness, competence). The study procedure was approved by the Institutional Review Board of the New York State Psychiatric Institute, Columbia University, and Western Psychiatric Institute and Clinic where the study took place. The protocols and databases were designed to ensure complete confidentiality for the participants

7.1 FUNDAMENTOS ÉTICOS DEL ESTUDIO

7.1.1 Implicaciones Éticas en la Investigación de la Conducta Suicida

La investigación acerca de la conducta suicida tiene implicaciones éticas, fundamentalmente en el campo del estudio de la vulnerabilidad individual (Saiz 1999; Saiz 2000; Saiz and Ibáñez 2001). En el momento actual no existen variables o combinaciones de factores ni biológicos, ni psicosociales, con especificidad suficiente para identificar a los pacientes con ideación suicida que podrían realizar una tentativa o consumir el suicidio (Pokorny, 1983; Seguí Montesinos 1989). Aún así éste es, precisamente el objetivo de la investigación: el reconocimiento de los factores que incrementan el riesgo de llevar a cabo una conducta suicida, con el fin de prevenir y disminuir la frecuencia de la conducta. La investigación en el suicidio pretende, de este modo mejorar las bases de la intervención biológica y clínica sobre el paciente suicida para lo cual es imprescindible:

- Realizar un óptimo diagnóstico y tratamiento de las enfermedades psiquiátricas
- Valorar detalladamente el riesgo suicida
- Implantar las medidas que dificultan el acceso a medios potencialmente letales y el tratamiento para atenuar los factores responsables de la vulnerabilidad del paciente para el suicidio (Beskow 1979).

7.1.2 Consentimiento Informado

El consentimiento informado constituye un documento ideal para preservar los derechos del paciente y también del acto médico. En investigación este documento se encarga de informar minuciosamente y de forma simple y accesible al usuario de que toda o parte de la información extraída va a ser tratada con fines exclusivamente científicos, garantizándose la confidencialidad de los datos.

En la valoración de los pacientes del presente estudio se cumplieron las tres condiciones del consentimiento informado (Barcia & Pozo 1998):

- Voluntariedad: los pacientes decidieron libremente su participación sin presión externa por parte del equipo investigador.
- Información: se les facilitaba una breve descripción de la investigación y sus objetivos y también se resolvieron las dudas que pudieran surgir.
- Competencia: los individuos seleccionados debían tener la capacidad suficiente para tomar la decisión acerca de su participación en este proyecto y las cuestiones que les afectaban como consecuencia: extracción de sangre, análisis de datos, confidencialidad y recepción de información sobre los resultados.

7.1.3 Confidencialidad

Los protocolos y la base de datos fueron manipulados exclusivamente por los estadísticos, médicos y psicólogos que participaron en este estudio. Los pacientes se identificaron con un código, para no usar los nombres de los sujetos en los procedimientos estadísticos y en las muestras enviadas al laboratorio. Los datos se almacenaron en un archivo informático protegido con un código de seguridad al que sólo tuvieron acceso los investigadores del estudio. Los participantes en el estudio podían solicitar un informe con los resultados de los análisis de sangre llevados a cabo.

7.2 DISEÑO DE LA INVESTIGACIÓN

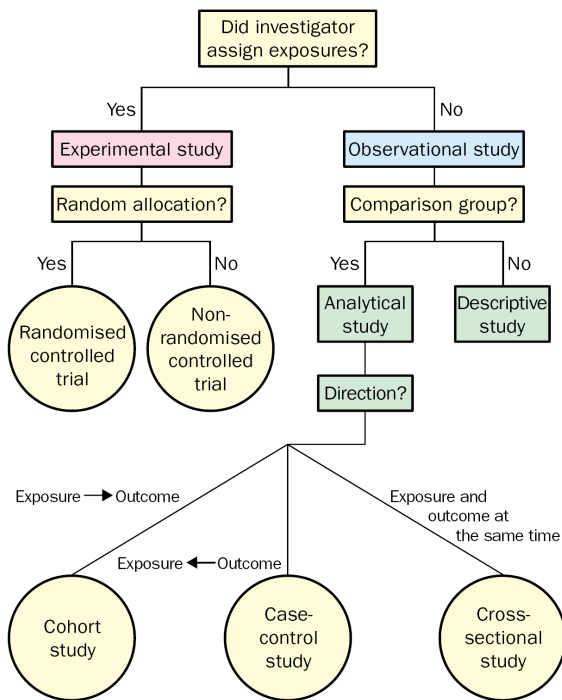
7.2.1 Descripción del Diseño

Los diseños de los estudios de investigación se clasifican según tres aspectos (Grimes and Schulz 2002; Kramer and Boivin 1987):

1. Direccionalidad: orden en el que la exposición y el resultado son investigados.
 - a. Prospectivos (seguimiento): cohortes.
 - b. Retrospectivos: Casos-control.
 - c. Simultáneos: cortes transversales.
2. Selección de la muestra: criterio de selección de la muestra:
 - a. Exposición.

- b. Resultado.
 - c. Otros.
3. **Temporalidad:** relación entre el momento del estudio y el momento de la exposición y resultado.
- a. Históricos.
 - b. Concurrentes.
 - c. Mixtos.

Figura 2. Taxonomía de los estudios (Lehmann y cols. 1995)



7.3 Subjects

Each hypothesis was tested in a subsample of a main sample of 430 patients with a Major Depressive Episode (Unipolar or Bipolar type).

7.3.1 Clinical Predictors of Suicidal Acts After a Major Depressive Episode in Affective Disordered patients

Patients who presented for treatment of major depressive episode and who were age 18–75 years were eligible for inclusion in the study. A total of 308 patients with a DSM-III-R major mood disorder (79% with major depressive disorder and 21% with bipolar disorder) based on the Structured Clinical Interview for DSM-III-R (SCID) (Spitzer y Williams, 1985) were enrolled in the study after giving written informed consent. The study was approved by the Institutional Review Board of the New York State Psychiatric Institute, Columbia University, and Western Psychiatric Institute and Clinic. Eighty percent of the study patients were recruited as inpatients. All patients had a physical examination and routine blood tests, including a urine toxicology screen. Exclusion criteria were current substance or

alcohol abuse, neurological illness, or active medical conditions that could confound diagnosis and the clinical characterization of psychopathology. After discharge, the subjects who had been recruited as inpatients received treatment as usual in the community. Patients were evaluated after 3 months, 1 year, and 2 years. An in-depth assessment of suicidal behavior during the intervening time period was conducted by using the Columbia Suicide History Form (Oquendo y cols., 2003b), which records self-reported data on number, method, and degree of medical damage of suicidal acts.

7.3.2 Sex Differences in Clinical Predictors of Suicidal Acts After a Major Depressive Episode in Affective Disordered Patients

Written informed consent was given by 184 female and 130 male patients, ages 18–75 years, who had major depressive disorder or bipolar disorder according to the Structured Clinical Interview for DSM-III-R (Spitzer y cols., 1990) and were seeking treatment of a major depressive episode; 80% were inpatients. The exclusion criteria were current substance or alcohol abuse and active medical conditions that could confound characterization of psychopathology and diagnosis.

The patients received naturalistic treatment in the community and were evaluated 3 months, 1 year, and 2 years after discharge.

There were no differences in age, sex, inpatient status, suicide attempt history, cluster B personality disorder, or depression severity between the patients lost to follow-up and those who completed at least one assessment. Each follow-up interview assessed suicidal behavior during the intervening time period.

7.3.3 Adequacy of Antidepressant Treatment

The subjects were 136 inpatients who were admitted for treatment to one of two university hospitals (in New York City and Pittsburgh) and who met the DSM-III-R criteria for a unipolar major depressive disorder, according to the Structured Clinical Interview for DSM-III-R (Spitzer y cols., 1990). The exclusion criteria were neurological illness or insult, an active medical condition, or substance or alcohol abuse or dependence within 6 months of admission. All subjects provided written informed consent as required by the institutional review board of each hospital.

7.3.4 Role of Life Events in Precipitating Suicidal Behavior

Patients aged 18 to 72 years with a DSM IV Major Depressive Episode (Unipolar or Bipolar type) (n=430) were enrolled into the study after giving written informed consent approved by the Institutional Review Board. Patients had a

physical exam and routine blood tests, including urine toxicology. Exclusion criteria were current substance or alcohol abuse or dependence, or active medical conditions that could confound diagnosis.

7.4 Instruments

Axis I disorders were evaluated with the SCID (Spitzer y Williams, 1985), and axis II disorders were evaluated with the International Personality Disorder Examination (Loranger y cols., 1994) and the Structured Clinical Interview for DSM-IV Axis II Disorders (First y cols., 1996). Acute psychopathology during the 2 weeks before the evaluation was assessed. Objective depressive symptoms were assessed by a research clinician who used the 17-item Hamilton Depression Rating Scale (Hamilton, 1960). Patients' subjective perception of depression severity was assessed by means of self-report with the Beck Depression Inventory (BDI, Beck y cols., 1961). The presence and severity of psychosis were evaluated in the current episode by using the Brief Psychiatric Rating Scale (BPRS) (Overall y Gorham, 1962), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984a), and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984b). Lifetime aggression was measured with the Brown-Goodwin Aggression Scale (BGA, Brown y cols., 1979) and the Buss-Durkee Hostility Inventory (BDHI, Buss y Durkee, 1957). Impulsivity was measured with the Barratt Impulsivity Scale (BIS, Barratt, 1965). Life stressors were measured by using the St. Paul-Ramsey Questionnaire (available from the authors), which rates the severity of individual stressors from 1 (none) to 7 (catastrophic) in six categories ranging from marital to occupational and gives a final global measure of the stressors. Hopelessness was measured with the Beck Hopelessness Scale (BHS, Beck y cols., 1974). The Reasons for Living Inventory (RFLI, Linehan y cols., 1983) was used to assess possible protective factors against suicide attempts. A history of childhood physical or sexual abuse and traumatic brain injury were rated as present or absent. Substance use disorders were diagnosed by using the SCID, and cigarette smoking was assessed by the subject's report of the number of cigarettes the subject smoked per day on average over the past 3 months.

A suicide attempt was defined as a self-destructive act with some degree of intent to end one's life. The number, method, and degree of medical damage of suicide attempts were recorded on the Columbia Suicide History Form (Oquendo y cols., 2003b). Suicidal ideation was characterized by using the Scale for Suicide Ideation (SSI, Beck y cols., 1979). Suicide attempts were characterized by using the Suicide

Intent Scale (SIS, Beck y cols., 1975) and the Lethality Rating Scale (LRS, Beck y cols., 1975), which assessed the patient's expectation regarding the outcome of the suicidal behavior and degree of medical injury resulting from the attempt, respectively.

7.4.1 Datos Sociodemográficos

Las variables recogidas en este epígrafe fueron: lugar y fecha de nacimiento, estado civil, número de hijos, convivencia, procedencia, nivel educativo, fuente de ingresos, profesión, situación laboral y orientación sexual.

7.4.2 Historia Médico-quirúrgica del Paciente y sus Familiares

Se incluyeron los antecedentes de enfermedades somáticas y mentales. Se permitió registrar tantos diagnósticos como fuese necesario.

Se emplearon las tablas y el sistema de codificación de psicofármacos del ATHF (*Antidepressant Treatment History Form*) elaborado por Oquendo y cols. (2003b) para registrar los fármacos que estaba tomando el paciente.

Se interrogó también a los pacientes por el número de ingresos médicos, quirúrgicos y psiquiátricos, así como por la frecuencia de utilización de los recursos asistenciales ambulatorios y dispositivos de urgencias.

En el apartado de antecedentes familiares somáticos y psiquiátricos, la entrevista se interesó por la existencia de enfermedades en familiares de primer grado y se pedía al paciente que especificara si conocía dichas enfermedades.

7.4.3 Problemas Psicosociales y Ambientales

Siguiendo las recomendaciones del DSM-IV (American Psychiatric Association 1995), se registraron los problemas psicosociales y ambientales que habían estado presentes durante el mes anterior a la evaluación actual. Se utilizó la clasificación que propone el DSM-IV para registrar estos eventos en su eje IV (American Psychiatric Association 1995). Además, los acontecimientos vitales acaecidos en el mes previo fueron evaluados mediante un instrumento específico (*St. Paul Ramsey Life Experience Scale*) (Roy y cols., 1986), que recoge información sobre los mismos, precisa cuál es el área implicada y la gravedad de los mismos. Simultáneamente, se valoró el grado en que el conjunto de actividades vitales contribuían al estado que presentaba el paciente en el momento de realizar el intento de suicidio.

También se evaluó, en cada paciente, la existencia de historia de privación parental y de maltrato en la infancia o la edad adulta. La posibilidad de que el paciente fuera adoptado fue también valorada específicamente.

7.4.4 Escala de Evaluación de la Actividad Global (EEAG)

El nivel general de actividad del sujeto se valoró usando la Escala de Evaluación de la Actividad Global (EEAG o *Global Assessment Scale*, GAS) (Endicott y cols., 1976), propuesta por el DSM-IV (American Psychiatric Association 1995) para la valoración del eje V (actividad global). Esta escala maneja un rango de puntuaciones (de 0 a 100, en tramos de 10 puntos) con relación a la actividad psicosocial, social y laboral. En la valoración de este aspecto, no se deben incluir alteraciones de la actividad debidas a limitaciones físicas (o ambientales).

Se puntuó la escala de acuerdo a la actividad global previa al intento de suicidio. No se consideró su puntuación en el momento de la tentativa, puesto que la escala recoge en uno de sus apartados la conducta suicida y le da el valor mínimo de la escala, lo cual invalidaría su uso en este estudio.

7.4.5 Valoración de Agresividad

En este estudio, se administró el inventario de antecedentes de conductas agresivas elaborado por Brown y Goodwin (*Brown-Goodwin Inventory*) (Brown y cols., 1979). Dicho inventario consta de 11 preguntas acerca de una gama tan variada de conductas agresivas como: problemas disciplinarios en la escuela, problemas con los profesores, sentirse enfadado, problemas con las figuras de autoridad en el trabajo, discusiones graves con los familiares, peleas, si ha destrozado algo de su propiedad, actos contra la ley, problemas con la policía, daños a otros con armas o autoagresiones. Se registra la frecuencia de dichas conductas como: nunca, rara, ocasional y frecuente, puntuándose de 0 a 3 en este orden. Estas conductas pueden aparecer en la infancia, en la adolescencia y/o en la edad adulta, por lo que dicha puntuación se considera para cada una de estas franjas de edad. En el presente estudio, se obtuvo finalmente: a) una media de puntuaciones para cada uno de los *ítems* considerando conjuntamente las tres franjas de edad; b) una media de la puntuación de los once *ítems* para cada franja de edad; c) la media de la puntuación total del cuestionario (para las tres franjas de edad), excluyendo la puntuación obtenida en la última pregunta (que investiga acerca de la existencia de autoagresiones en el pasado); d) la media de la puntuación total del cuestionario para todas las franjas de edad sin excluir la puntuación obtenida en la pregunta acerca de las autoagresiones; y, e) la suma total de las medias obtenidas para las tres franjas de edad.

También se utilizó el Buss-Durkee Hostility Inventory (Buss y Durkee, 1957).

7.4.6 Evaluación de Impulsividad

Se evaluó la impulsividad como dimensión de la personalidad (impulsividad como rasgo (Frosch y

Wortis 1954; Szerman 2002), mediante la undécima versión de la escala de impulsividad de Barrat (*Barrat Impulsivity Scale*, escala BIS-11) (Barratt y Stanford 1995). Esta escala consta de treinta preguntas que pretenden evaluar la impulsividad considerada como una forma de actuar y pensar. A cada una de las preguntas se responde haciendo referencia a la frecuencia: raramente o nunca, ocasional, a menudo, siempre o casi siempre. Se puntuó de 0 a 4 por este orden. Se reconoció la existencia de tres factores independientes: impulsividad cognitiva, impulsividad motora y ausencia de planificación (Barratt 1985; Patton y cols., 1995).

Finalmente, se consignó la puntuación total obtenida en el BIS-11 (Oquendo y cols., 2001).

7.4.7 Valoración de la Conducta Suicida

Las escalas de valoración del intento de suicidio tienen como objetivo identificar los pacientes con mayor riesgo de cometer suicidio, si bien tienen el inconveniente de su pobre especificidad (Sarró y Cruz 1997). No obstante, numerosos autores defienden el empleo sistemático de instrumentos semiestructurados de *screening* para la detección de riesgo de suicidio en la exploración psicopatológica de rutina (Malone y cols., 1995b), aunque la valoración final descansa en el juicio clínico del médico.

Las escalas de suicidio se pueden clasificar en dos grupos (Díaz-Suárez y cols. 1992):

1. Escalas no específicas que valoran síntomas o síndromes asociados
2. Escalas específicas que valoran directamente ideas o conductas suicidas, tanto en pacientes con ideación como en las tentativas.

Los problemas derivados del uso de escalas son (Kreitman 1987):

- No miden factores exclusivos de la conducta suicida.
- En la conducta suicida convergen un gran número de variables.
- Las escalas no son capaces de vincular la valoración del riesgo a un margen de tiempo.
- Los instrumentos diseñados para una población atendida en un medio a menudo no son trasladables a otras.

7.4.7.1 Intencionalidad Suicida: Suicide Intent Scale (Beck y Kovacs 1979).

Beck ha desarrollado varias escalas para la valoración de la conducta suicida. En el presente estudio, se utilizó la Escala de Tentativa Suicida de Beck (*Suicide Intent Scale*, SIS) (Beck y Kovacs 1979), empleada para valorar las características y la seriedad de la tentativa. Tiene dos secciones: en la primera se recogen las circunstancias en las que se lleva a cabo (circunstancias objetivas); en la segunda se valora la actitud del paciente ante la vida y la muerte y la

consideración que tiene el paciente de la tentativa. El conjunto de las secciones se compone de 15 *items* valorados de 0 a 2. En los trabajos realizados para la validación de la escala, la media de las puntuaciones para riesgo elevado es 16.3, 10.1 medio y 6.7 bajo.

La escala (*Suicide Intent Scale*) de Beck (Beck y Kovacs 1979) se hace durante de la entrevista psiquiátrica.

Al margen de la parte puntuable (2 secciones), la escala recoge información relacionada con el método del intento y la posible crítica al mismo. Se considera también la fiabilidad de las respuestas proporcionadas por el paciente.

7.4.7.2 Letalidad

La letalidad se puede valorar de forma objetiva, considerando las consecuencias médicas del intento. Así, se puede clasificar la gravedad médica del intento en muy grave (fracturas múltiples, alteración del nivel de conciencia que precisa atención en unidad de cuidados intensivos), grave (precisa hospitalización) y leve (las lesiones no precisan ingreso en unidad médico-quirúrgica) (Nieto-Rodríguez y cols. 1992). La letalidad del intento fue codificada de ese modo de acuerdo con la *Lethality Rating Scale and Method Attempt Coding* (Beck, Resnik, y Lettieri 1974). Se considera la puntuación de 0 (no letal) hasta 8 (muerte). En el presente estudio se dividió la letalidad del intento en dos grados: alta y baja, considerando como punto de corte una puntuación mayor de dos en la escala *Lethality Rating Scale and Method Attempt Coding* (Beck, Resnik, y Lettieri 1974).

Se preguntó también por la intencionalidad letal o letalidad subjetiva (esto es, la expectativa del paciente sobre la posibilidad del desenlace fatal de su conducta) en algunas de las cuestiones de las escalas que se administraban posteriormente. En un reciente estudio de nuestro equipo de investigación se descubría la existencia de dos factores en la Escala de Suicidio de Beck en los pacientes con intentos de suicidio: *letalidad esperada* (preguntas 4,9,10,11,12,13 y 14 del SIS) y *planificación* (preguntas 1,2,3,5,6,7 y 8 del SIS (Beck y Kovacs 1979; Díaz, 2003).

De cara a la evaluación del riesgo de reintento, se exploró si el paciente criticaba el intento y su intención de repetirlo, así como por la existencia de planes de cara al futuro.

7.4.7.3 Otras Características de la Tentativa

Para valorar otras características del intento, se le preguntó al paciente acerca de: previsión de salvamento, existencia de pensamientos suicidas (bien como ideas delirantes, de imposición o sobre un trasfondo depresivo, bien como impulsos), si fue interrumpido, si sintió alivio al salvarse y también se le pidió que describiera cómo ocurrió. El método empleado fue codificado de acuerdo con la *Lethality Rating Scale and*

Method Attempt Coding (Beck, Resnik, y Lettieri 1974), que valora los diversos métodos empleados teniendo en cuenta también las consecuencias médicas del intento.

7.4.7.4 Antecedentes Familiares de Conducta Suicida: Familiar Suicide History (Beck, Resnik, y Lettieri 1974).

Esta escala recoge información sobre el parentesco que une al familiar con antecedentes de conducta suicida con la paciente en estudio, el número de intentos, el método, la letalidad (codificados ambos con el LRS) (Beck, Resnik, Lettieri 1974), y el resultado del mismo. Al mismo tiempo, se da cabida a la evaluación de otros intentos de suicidio en personas cercanas a la paciente aunque no sean familiares biológicos.

7.4.7.5 Antecedentes Personales de Conducta Suicida.

En el presente trabajo, se empleó la escala *Columbia Suicide History Form* (Oquendo y cols., 2003b), recogiendo información de interés sobre el primer intento de suicidio que recordaba el paciente, sobre el más reciente y sobre el más letal. De cada uno de ellos, se interroga por aspectos relativos a los acontecimientos desencadenantes (*St. Paul Ramsey Life Experience Scale*) (Roy y cols., 1986), las circunstancias en que se produjo, el medio utilizado, la letalidad (ambos aspectos son codificados mediante la escala *Lethality Rating Scale and Method Attempt Coding* (Beck, Resnik, y Lettieri 1974)), las consecuencias médicas, y las expectativas del paciente en cuanto al resultado del acto suicida (mediante la *Suicide Intent Scale*, Beck y cols., 1975).

7.4.7.6 Factores Protectores.

Se preguntó al paciente sobre la presencia de convicciones religiosas y por la existencia de apoyo en el medio familiar y en el entorno social. Se utilizó la escala *Reasons for Living Inventory* (Linehan y cols., 1983).

7.4.8 Valoraciones Prospectivas Durante el Periodo de Seguimiento

Tras el alta, los pacientes fueron evaluados a los 3 meses, 1 año y 2 años. Los participantes recibieron el tratamiento ambulatorio habitual. Cada valoración a lo largo del seguimiento documentó la ocurrencia de actos suicidas, la presencia o ausencia de un episodio de depresión mayor y de acontecimientos vitales estresantes durante el periodo entre valoraciones. También se recogieron los nombres de los fármacos y la duración del tratamiento.

7.4.8.1 Assessment of Adequacy of Antidepressant Treatment

The adequacy of antidepressant treatment was assessed by using the Antidepressant Treatment History Form (Sackheim y cols., 1990). This instrument is used to score the adequacy of

treatment trials for major antidepressant medication categories and ECT on a scale from 0 to 5 and has good reliability and validity (Sackheim y cols., 1990; Prudic y cols., 1996). A score of 3 or above is considered adequate treatment unless the patient responds to a lower dose. In this study, adequacy was based on the calculated score for adequacy, rather than treatment response.

The minimum duration of an adequate antidepressant trial is defined as 4 weeks. Minimum adequate daily doses are 200 mg of imipramine hydrochloride, amitriptyline, desipramine, trimipramine, clomipramine, maprotiline, doxepin, or nomifensine; 76 mg of nortriptyline; 41 mg of protriptyline; 20 mg of paroxetine, fluoxetine, or citalopram; 200 mg of fluvoxamine; 100 mg of sertraline; 61 mg of phenelzine; 41 mg of selegiline, tranylcypromine, or isocarboxazid; 300 mg of moclobemide; 30 mg of mirtazapine; 225 mg of venlafaxine; 300 mg of nefazodone or bupropion; and 400 mg of trazodone. For ECT, the minimum is defined as more than six unilateral or bilateral treatments. Both duration and dose must be adequate for the trial to be classified as adequate. Treatments using a combination of antidepressants are rated according to the highest rating given to the individual antidepressants that are combined, except in the case of lithium augmentation, when a rating of 3 or 4 is increased by 1 point.

7.4.8.2 Assessment of Life Events

The Recent Life Changes Questionnaire (RLCQ), a well-validated and reliable instrument [1, 2], was used to document both positive and negative life events. This instrument gathers information about the past year, divided in 3-month blocks. It covers the occurrence of 5 different types or domains of life events: 1. Health, such as the occurrence of illness or injury; 2. Work, for example gain or loss of employment; 3. Home/Family, such as additions or losses of family members; 4. Personal/Social, for instance, changes in social activities, difficulties with the law and challenges with a significant relationship; and 5. Financial, such as major purchase or gain/loss of income.

7.5 Statistical Method

We conducted cross-sectional analyses comparing the clinical and demographic characteristics of past attempters and non-attempters at baseline. We conducted several prospective analyses. The first analysis included all risk factors found to be associated with a past history of suicidal behavior at baseline as independent variables and was conducted to generate a list of the most significant predictors of suicidal acts. In the second analysis, we examined the role of the two diathesis traits, aggression/impulsivity and the tendency for pessimism, in the likelihood of future suicidal

acts. A third analysis examined the effect of various risk and protective factors comparing males and females to detect sex differences. Two additional analyses examined time varying covariates during the follow up period. The first examined the effect of antidepressant medication prescribed during the follow up on suicide risk, while considering the occurrence of Major Depressive Episodes. The last prospective analysis examined the effects of stressful life events that occurred during the follow up period, on suicidal behavior while considering the occurrence of Major Depressive Episodes.

7.5.1 Cross-Sectional Analysis of Baseline Characteristics

Clinical and demographic characteristics of past attempters and non-attempters at baseline were compared using two sample t-tests for quantitative variables and chi-squared statistics for categorical variables. Fisher's exact test was used for tables with low expected cell counts.

To reduce the dimensionality of the baseline data, two Principal Component Analyses were implemented to obtain aggression/impulsivity factors and pessimism factors based on baseline characteristics. We previously reported that these factors predicted increased risk for future suicide attempt [3]. Briefly, the aggression/impulsivity factors were derived from the Barratt Impulsivity Scale, the Buss-Durkee Hostility Inventory, and the Brown-Goodwin Aggression History Scale. The first two factors explained 83% of the variability and were retained for further analysis. For calculating the pessimism factors, we first adjusted for objective (physician-measured) severity of depression by performing individual linear regressions of the total scores on the Beck Depression Inventory, the Beck Hopelessness Scale, the Reasons for Living Scale, and the Scale for Suicidal Ideation, on the total score from the Hamilton Depression Rating Scale-17 (HDRS-17). Residuals were entered into a Principal Component Analysis, and the first two factors, explaining 75% of the total variance, were retained for further analysis.

7.5.2 Analysis of Clinical Predictors of Suicidal Acts After a Major Depressive Episode in Affective Disordered Patients

Since a history of suicide attempt is the most powerful predictor of future suicidal acts, the clinical and demographic characteristics of suicide attempters and nonattempters at baseline were compared by using two-sample t tests and chi-square tests, as appropriate. Relationships between variables were examined in this manner as well. Putative risk factors for future attempts included the variables for which significant differences between attempters and nonattempters were found at baseline and additional variables

identified in the literature as risk factors for suicidal acts. The variables for which significant differences between attempters and nonattempters were found at baseline were age; presence of a cluster B personality disorder, childhood history of abuse, substance abuse, and traumatic brain injury; and scores on the Beck Depression Inventory, Scale for Suicide Ideation, Reasons for Living Inventory, Brown-Goodwin Aggression Scale, Buss-Durkee Hostility Inventory, and Barratt Impulsivity Scale. The literature supported the addition of sex, marital status, cigarette smoking, and scores on the Hamilton depression scale, Beck Hopelessness Scale, BPRS, SANS, and SAPS. Both sets of variables were entered into a single Cox proportional hazards regression analysis to assess the relative importance of risk factors in predicting a future suicidal act. Continuous variables were dichotomized by median split to facilitate interpretation.

7.5.3 Analysis of Sex Differences in Clinical Predictors of Suicidal Acts After a Major Depressive Episode in Affective Disordered Patients

Clinical and demographic characteristics of both sexes at baseline were compared by means of two-sample t tests, nonparametric Wilcoxon tests, and chi-square statistics as appropriate. Second, sex differences in the time to a suicidal act were tested by a Cox proportional hazards regression model. Third, for each sex, the risk of suicide attempt or completion in the 2-year follow-up period was evaluated by using univariate Cox analysis with time to first attempt as the dependent variable and putative risk factors as predictors. Scale and continuous variables were entered as linear effects. Finally, a Cox multivariate analysis with all significant risk factors as predictors assessed the relative importance of these factors in predicting a future suicidal act for men and women separately.

7.5.4 Analysis of Prospective Data to Determine the Adequacy of Antidepressant Treatment

During the follow-up period, the time-varying data were the adequacy of antidepressant treatment and the presence or absence of major depression. These data were used to divide the follow-up period into epochs. The first epoch started the day after discharge from the inpatient unit and continued until the time-varying data changed. A new epoch started whenever there was a change in adequacy of antidepressant treatment, a change in depression status (present or absent), or both. Thus, each epoch has a constant clinical state (presence or absence of depression) and a constant treatment adequacy rating. A suicidal act, withdrawal from the study, or completion of the 2-year follow-up period marked the end of the final epoch.

Cox's proportional hazards analysis with time-varying covariates was used to model the risk of a suicide attempt during the follow-up period. This analysis provides a hazard ratio for subjects in two groups. The hazard ratio at time t is the ratio of the probabilities that two given subjects, one from each group, having not made an attempt in t days since discharge, will make an attempt shortly thereafter. Under the proportional hazard assumption, which is compatible with our data, this ratio is constant in time.

Two models were constructed. The first model examined baseline characteristics to determine whether variables cited as predictors in the literature (sex, age, and total lifetime number of suicide attempts at study entry) identified subjects likely to attempt suicide in the future. The interaction between age and number of lifetime attempts was also entered into the model. A second model contained baseline variables found to be significant in the first model (age and total lifetime number of suicide attempts at study entry) and the time-varying covariates, namely intensity of antidepressant treatment, depression status (major depression present or absent in each month since last evaluation), and their interaction. Two-sample t tests were used to compare the average intensity of treatment in the follow-up period for subjects with a baseline suicide attempt and subjects with no baseline suicide attempt; comparisons were made for the follow-up period as a whole, periods of active depression, and periods free of depression. Further, because of the additional risk for suicidal behavior conferred by borderline personality disorder, we compared the adequacy of treatment during the follow-up period for patients with and without comorbid borderline personality disorder.

7.5.5 Analysis of Prospective Data to Determine the Role of Life Events in Precipitating Suicidal Behavior

During the follow-up period, time-varying covariates were the presence or absence of recent life events and the presence or absence of MDE. These data were used to divide the follow-up period into epochs for each subject. The first epoch started the day after initiation of outpatient care. A new epoch started whenever there was a change in life events, a change in depression status or a suicide attempt. Thus, each epoch has a constant clinical state (presence or absence of depression) and a life event rating. Withdrawal from the study or completion of the two-year follow-up period marked the end of the final epoch for each subject. Epoch lengths varied both between and within subjects, thus this data set could not be expressed in person-month form.

To test our hypothesis that both MDEs and recent life events are risk factors for subsequent suicide attempts, independently from each other and from

previously used baseline risk factors like female sex, younger age, and the pessimism and aggression factors [3], data on suicide attempts during the follow-up period was analyzed using the Andersen-Gill extension to the Cox proportional hazards regression model (Andersen and Gill, 1982). This method is appropriate to analyze multiple events per person, time-varying covariates constant over time intervals of different lengths, and censored times in study. It assumes that the number of events in non-overlapping time intervals is independent, given the covariates (Therneau & Grambsch, 2000).

The data analysis plan was as follows: first, the total stress score from the Recent Life Changes Questionnaire [1, 2] was used in conjunction with the MDE indicator and the above baseline variables to predict suicide attempt in the respective epoch. Then, total stress scores for each of the five domains described above were used in separate models, along with presence/absence of an MDE and the baseline predictors. Significance levels were adjusted for multiple testing using the Bonferroni method.

To discover which, if any, of the individual items were risk factors for future suicide attempt, we tested each item of the RLCQ individually as a predictor, while controlling for major depressive

episode, age, sex, aggression, and pessimism factors. One sided significance tests in the direction of risk were used, since many of the stress items were related to rare events and power was limited. Significance levels were adjusted for multiple testing using the Benjamini-Hochberg linear step-up procedure, rather than the Bonferroni adjustment. This method controls the False Discovery Rate (the ratio of false hypotheses out of all that are rejected), rather than the experiment-wise Type I error rate, and is more appropriate when the goal is discovery, rather than confirmatory analysis. We used a global FDR=15% as a cutoff.

We also built two Generalized Linear Models with MDE and RLC as longitudinal responses, respectively, with the baseline variables described above as predictors.

Kaplan-Meier estimates of the cumulative hazard function for suicide attempt, and B-spline estimates of the time curves for the proportion of subjects within a MDE or experiencing stressful life events were graphed side by side to enable easy comparison of the time trends.

8 RESULTS

Abstract

The three most powerful predictors of future suicidal acts were a history of suicide attempt, subjective rating of the severity of depression, and cigarette smoking, each of which had an additive effect on future risk. The pessimism and aggression/impulsivity factors both predicted suicidal acts, and each factor showed an additive effect.

For women, the risk for future suicidal acts was sixfold greater for prior suicide attempters; each past attempt increased future risk threefold. Suicidal ideation, lethality of past attempts, hostility, subjective depressive symptoms, fewer reasons for living, comorbid borderline personality disorder, and cigarette smoking also increased the risk of future suicidal acts for women. Among men, past drug abuse, family history of suicidal acts, cigarette smoking, borderline personality disorder and early parental separation each more than tripled the risk of future suicidal acts. Aggression, hostility and past suicidal behavior did not significantly predict future suicidal acts for men. Multivariate analyses uncovered that among depressed men the predictive power of several of the variables could be explained by their relationship to the increased risk ascribable to cigarette smoking.

Major depression in the followup period increased the risk of a suicide attempt sevenfold. For each suicide attempt in a subject's history, the risk for an attempt in the follow-up period increased by 30%. Antidepressant treatment during the follow-up period was mostly inadequate. Consequently, a relationship between adequacy of antidepressant treatment during follow-up and the risk of a suicide attempt could not be found. Furthermore, subjects with a history of a suicide attempt at baseline were not treated more vigorously than nonattempters.

Prospectively, several variables controlling for life events predicted future suicidal acts: subjective depression, suicidal ideation, hopelessness, low reasons for living, cigarette smoking and a past history of suicidal behavior. Pessimism and past history of suicide attempt at baseline, but not aggressive/impulsivity predicted future suicidal acts. The occurrence of an episode of major depression had an important effect on the risk for suicidal acts as well, but life events did not, nor was there an interaction between these two variables.

8.1 Descripción Muestral

Las distintas hipótesis se han contrastado con submuestras de una muestra principal que se describe a continuación en terminos sociodemográficos y psicopatológicos (tabla 2).

Tabla 2. Características de las Submuestras Empleadas en cada Hipótesis.

Hypotheses	Attempter	Mood	Time years	Event Rate
Predictors	104 F 59 M	80 F 64 M	2	15.0%
Sex differences	109 F 62 M	75 F 58 M	2	16.6%
Treatment adequacy	74	62	2	15.0%
Life events	132 F 88 M	117 F 93 M	2	9.5%

Las muestras analizadas tenían una proporción similar de hombres:mujeres (1:1.5) con el mismo tiempo de seguimiento (2 años) y un porcentaje similar de conducta suicida (intentos y suicidios consumados) durante el seguimiento (9.5-16.5%). Todos los pacientes estaban diagnosticados de trastornos afectivos (depresión mayor o trastorno bipolar), y se consideraba el grupo de casos el constituido por aquellos con antecedentes de intentos, según la definición de suicidio de O'Carroll y cols. (1996), cuyo tamaño muestral es ligeramente superior al de controles (pacientes con trastornos afectivos sin historia de intentos de suicidio). Ninguno de los pacientes sin

antecedentes de intento de suicidio falleció a causa de suicidio durante el periodo de seguimiento.

8.1.1 Sociodemográficos

La edad de todos los pacientes era mayor o igual a 18 años. La media de edad era ligeramente inferior en los pacientes con antecedentes de intentos de suicidio ($m=36.3\pm 11.0$) con respecto a los pacientes sin antecedentes de intentos de suicidio (40.1 ± 12.2) ($t=-3.36$, $p=0.0009$) (tabla 3). No había diferencias estadísticamente significativas en la distribución por sexos de las dos muestras ($\chi^2=0.81$, $gl=1$, $p=0.3682$), siendo la proporción de hombres en las dos muestras del 40% y 44% respectivamente.

El número de eventos vitales estresantes medidos con la escala de St. Paul-Ramsey fue mayor en pacientes con antecedentes de intento de suicidio (2.1 ± 0.8) que en los pacientes que no tenían antecedentes de intento de suicidio (1.8 ± 0.7) de una forma estadísticamente significativa ($t=3.11$, $p=0.002$).

La presencia de antecedentes de abuso infantil era superior en los pacientes con intento de suicidio (53% vs 38%) ($\chi^2=8.42$, $gl=1$, $p=0.0037$), sin embargo la proporción de separación de los padres por debajo de los 15 años era muy similar (35% vs 36%) ($\chi^2=0.02$, $gl=1$, $p=0.8773$).

8.1.2 Diagnósticos Psiquiátricos

La media de las puntuaciones de la escala de depression de Hamilton fue similar en los dos grupos del estudio (pacientes con intentos de suicidio 19.8 ± 6.1 vs pacientes sin intentos 18.9 ± 6.1) ($t=1.52$; $p=0.1292$). Sin embargo, la

puntuación fue mayor en el grupo de pacientes con intentos de suicidio (28.2±12.1) que en los que no tenían intentos (25.2±10.5) de forma significativa (t=2.76; 0.0059) usando la escala de depresión de Beck.

La prevalencia de trastornos por consumo de sustancias comórbido es significativamente mayor (Chi²=9.16, gl=1, p=0.0025) en el grupo de pacientes con antecedentes de intento de suicidio (48%) que en el de los pacientes sin antecedentes de intento de suicidio (34%). En el consumo de cigarrillos la diferencia (38% vs 31%) no llegaba a alcanzar la significación estadística (Chi²= 2.83, gl=1, p= 0.0926).

Tabla 3. Baseline Comparison of Depressed Past Suicide Attempters and Non-attempters: Demographics, Current Psychopathology and Trait Assessments (Full sample, N=430)

	Attempter (N=220)	Mood (N=210)	T-test (Chi²)	p-value
Age (years)	36.3±11.0	40.1±12.2	-3.36	0.0009
Male (%)	88/220 (40%)	93/210 (44%)	(0.81)	0.3682
Hamilton Depression Rating Scale	19.8±6.1	18.9±6.1	1.52	0.1292
Beck Depression Inventory	28.2±12.1	25.2±10.5	2.76	0.0059
St. Paul-Ramsey Questionnaire	2.1±0.8	1.8±0.7	3.11	0.002
Childhood abuse (%)	104/197 (53%)	77/201 (38%)	(8.42)	0.0037
Childhood Separation under 15 (%)	76/218 (35%)	74/208 (36%)	0.02	0.8773
Comorbid past substance abuse (%)	106/220 (48%)	71/210 (34%)	(9.16)	0.0025
Cigarette Smoking (%)	84/219 (38%)	64/209 (31%)	(2.83)	0.0926
Borderline Personality Disorder	90/219 (41%)	25/208 (12%)	(45.83)	<0.0001
Bipolar Disorder (vs. MDD)	79/219 (36%)	52/208 (25%)	(6.15)	0.0131
Aggression				
Brown-Goodwin History of Aggression	22.1±6.0	18.7±5.0	5.59	<0.0001
Buss-Durkee Hostility Inventory	37.8±11.9	34.0±11.6	3.13	0.0019
Barratt Impulsivity Scale	54.0±16.8	51.6±16.2	1.4	0.1623
Factor1	0.23±1.04	-0.25±0.90	5.1	<0.0001
Factor2	0.00±1.04	0.00±0.96	-0.04	0.9663
Pessimism				
Hopelessness Scale	12.3±6.0	11.3±6.0	1.82	0.0687
Scale for Suicidal Ideation	17.7±10.4	8.4±8.9	8.67	<0.0001
Reasons for Living Scale 3	148.1±48.	167.3±41.1	-4.19	<0.0001
Factor1	0.05±1.03	-0.05±0.96	1.02	0.309
Factor2	0.31±0.99	-0.33±0.90	7	<0.0001

La comorbilidad con el trastorno límite de personalidad era superior en los pacientes con antecedentes de intento de suicidio (41% vs 12%) de forma estadísticamente significativa (Chi²= 45.83, gl=1, p<0.0001).

8.1.3 Puntuaciones en las Escalas de Impulsividad y Agresividad

Las puntuaciones en el inventario de antecedentes de conductas agresivas elaborado por Brown y Goodwin (*Brown-Goodwin Inventory*) (Brown y cols., 1979) eran superiores en los pacientes con antecedentes de intentos de suicidio (22.1±6.0 vs 18.7±5.0) (t=5.59; p<0.0001).

Estas puntuaciones concuerdan con las que registra el *Buss-Durkee Hostility Inventory*, que eran significativamente mayores en los pacientes con antecedentes de intentos de suicidio (37.8±11.9) que en los pacientes sin antecedentes de intentos de suicidio (34.0±11.6) (t=3.13; p= 0.0019).

La puntuación total en la Escala de Impulsividad de Barratt (Barratt y Stanford 1995) no era significativamente mayor en los pacientes con antecedentes de intentos de suicidio (54.0±16.8) que en los pacientes sin antecedentes de intentos de suicidio (51.6±16.2) (t=1.4; p<0.1623).

8.1.4 Puntuaciones en las Escalas de Pesimismo y Suicidio

Como es de esperar, los pacientes con antecedentes de intentos de suicidio presentaban una mayor ideación suicida (17.7±10.4) medida con la *Scale for Suicidal Ideation* que los pacientes sin antecedentes de intentos de suicidio (8.4±8.9) (t=8.67; p<0.0001). Lo contrario ocurría con la *Reasons for Living Scale*, donde las puntuaciones eran mayores en los pacientes sin antecedentes de intentos de suicidio (148.1±48.3 vs 167.3±41.1) de forma estadísticamente significativa (t=-4.19; p<0.0001).

Curiosamente, la diferencia entre las medias de las puntuaciones en la *Hopelessness Scale* (12.3±6.0 vs 11.3±6.0) no era estadísticamente significativa (t=1.82; p=0.0687).

8.2 Clinical Predictors of Suicidal Acts After a Major Depressive Episode in Affective Disordered Patients

8.2.1 Baseline Clinical Analysis

Depressed subjects with a history of suicide attempt (baseline attempters) and non-attempters did not differ significantly in terms of sex, education, number of children, employment status, or proportion married (Tabla 4).

Baseline attempters, however, were significantly younger than non-attempters. At index assessment, baseline attempters and non-attempters were similar in terms of objective severity of acute psychopathology (HDRS, BPRS, SANS, SAPS, length of current episode).

RESULTS

Tabla 4. Baseline Demographic Features of Suicide Attempters versus Non-attempters with Major Depression (N=308).

	Attempters (N=164)	Non-attempters (N=144)	t (Chi ²)	p-value
Age (yr)	35.5±10.5	39.1±12.8	-2.7	0.007
Total education (yr)	14.6±2.9	15.2±3.0	-1.87	0.063
Number of children	1.0±1.5	1.1±1.3	-0.68	0.490
% Male	59/163 (36%)	64/144 (44%)	(2.16)	0.140

Tabla 5. A Baseline Comparison of Depressed Past Suicide Attempters and Non-attempters: Current Psychopathology (N=308). * Wilcoxon's Test Z-score.

	Attempters (N=164)	Non-attempters (N=144)	t	p
Hamilton Depression Rating Scale	20.1±5.7	19.9±6.1	0.34	0.730
Beck Depression Inventory	29.8±11.6	26.1±10.9	2.8	0.006
Brief Psychiatric Rating Scale	35.3±8.1	36.5±8.0	-1.4	0.170
Scale for the Assessment of Positive Symptoms (SAPS)	1.1±2.4	1.5±2.7	-1.3	0.190
Scale for the Assessment of Negative Symptoms (SANS)	9.7±3.0	10.2±2.6	-1.5	0.140
Hopelessness Scale	12.5±5.8	11.4±5.8	1.7	0.090
Scale for Suicidal Ideation	16.9±10.8	8.9±8.6	7.1	<0.0001
Reasons for Living Scale	141.5±46.2	172.6±42.0	-5.4	<0.0001
St. Paul-Ramsey Scale	4.1±1.1	3.8±1.2	2.3	0.024
Length of current depressive episode (days)	Median=16.5	Median=20	0.6	0.530*

In contrast, baseline attempters showed more pessimism with higher ratings of subjective depression (BDI), fewer perceived reasons for living (RFLS) and more suicidal ideation (SSI) in the context of a depressive episode. Hopelessness (BHS) was not significantly different. Attempters also had higher scores on the St. Paul-Ramsey Scale at baseline, but the difference in life events was not clinically meaningful (Tabla 5).

Baseline attempters manifested more aggressive/impulsive traits reflected in elevated lifetime aggression scores (BGLHA and BDHI), impulsivity scores (BIS), and rates of Cluster B

personality disorder (Tabla 6). They were more likely than non-attempters to report a childhood history of abuse, past traumatic brain injury, and comorbid past alcoholism or substance abuse disorder. Baseline attempters were also more likely to have a first degree relative who had attempted or completed suicide. Moreover, subjective depression (BDI) was closely related to sex, objective depression (HDRS), impulsivity and, similarly to baseline attempter status, was related to suicidal ideation and reasons for living. Cigarette smoking was related to a history of substance or alcohol use disorder.

Tabla 6. A Baseline Comparison of Depressed Past Suicide Attempters and Non-attempters: Traits Measures (N=308).

	Attempters (N=164)	Non-attempters (N=144)	t (Chi ²)	p
Brown-Goodwin Life History of Aggression	19.9±6.0	16.8±4.7	4.95	<0.0001
Buss-Durkee Hostility Inventory	38.2±11.6	33.5±12.0	3.21	0.002
Cluster B Personality Disorder (%)	90/159 (56.6%)	36/135 (26.7%)	(26.7)	<0.0001
Barratt Impulsivity Scale	54.7±17.0	46.2±17.7	2.44	0.015
Reported childhood history of abuse (%)	68/132 (51.5%)	40/126 (32%)	(10.4)	0.001
History of Traumatic Brain Injury (%)	65/153 (42.5%)	38/136 (28.0%)	(6.6)	0.010
Comorbid past alcohol or substance abuse (%)	87/164 (53.1%)	57/142 (40.1%)	(5.1)	0.024
Cigarette Smoking	61/143 (42%)	49/123 (39%)	(0.2)	0.642
A first degree relative who attempted/completed suicide (%)	25/163 (15.3%)	10/144 (7%)	(5.3)	0.021

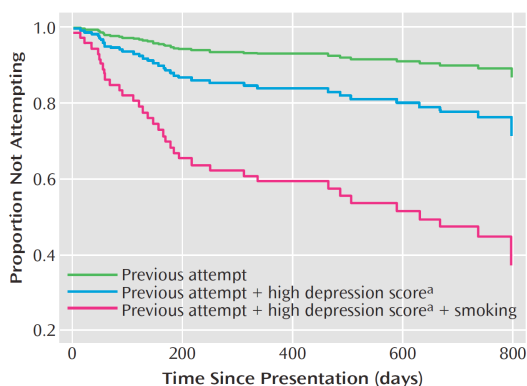
8.2.2 Prospective Clinical Predictors Analysis

Four subjects completed suicide and 38 attempted suicide during the two year follow-up period, representing 15% of the sample. Most suicidal acts took place in the first year, with the rate dropping dramatically after about 3-6 months. The rate in the second year remained elevated but steady (Figura 3).

A multivariate Cox Proportional Hazards analysis with all correlates of past suicide attempts and

additional risk factors identified from the literature showed that history of suicide attempt (Hazard Ratio [95% Confidence Interval]=4.41 [1.92, 10.12], $p<0.001$), higher subjective depression scores (BDI)(HR [95% C.I.] = 2.96 [1.39, 6.32], $p=0.005$) and cigarette smoking (HR [95% C.I.] = 2.35 [1.20, 4.59], $p=0.012$) were the three strongest predictors.

Figura 3. Cumulative Proportion of Patients Who Did Not Attempt Suicide Over a Two-Year Follow-Up Period After a Major Depressive Episode, by Baseline Presence of One, Two and Three of the Most Powerful Predictors of Suicidal Acts.



The effect of these predictors on risk of suicidal acts in the follow up period was additive (Figura 3). These three predictors were closely related to other risk factors using $p<0.01$ as the threshold for statistical significance (Figura 4).

Figura 4. Relationship Between the Three Strongest Predictors and Other Variables Related to a History of Suicidal Acts.

Previous Attempt	Higher Score on Beck Depression Inventory	Cigarette Smoking
Younger age	Female sex	Alcohol or other substance use disorder
Childhood history of abuse	Objective depression ^c	
Cluster B personality disorder	Hopelessness ^d	
Higher aggression ^b	Higher impulsivity ^e	
Suicidal ideation 2 weeks before intake		
Few perceived reasons for living ^f		

^a Relationships between variables were analyzed by using chi-square tests and t tests ($p<0.01$)

^b Measured with the Brown-Goodwin Aggression Scale and the Buss-Durkee Hostility Inventory. Scores were dichotomized as high or low by median split.

^c Measured with the 17-item Hamilton Depression Rating Scale.

^d Measured with the Beck Hopelessness Scale. Scores were dichotomized as indicating the presence or absence of hopelessness on the basis of a median split.

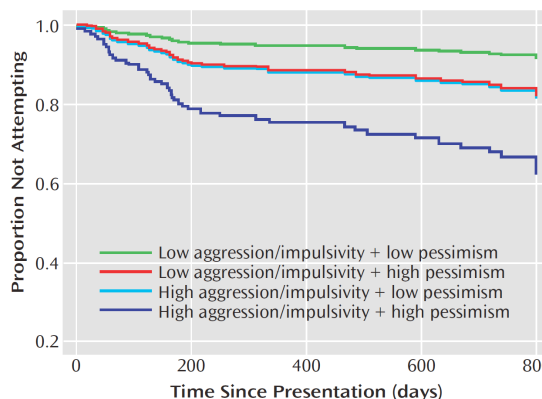
^e Measured with the Barratt Impulsivity Scale. Scores were dichotomized as high or low by median split.

^f Measured with the Reasons for Living Inventory. Numbers of reasons were dichotomized as high or low by median split.

8.2.3 Diathesis and Future Suicidal Behavior

High levels of both aggression/impulsivity (Odds Ratio=2.26, $z=2.43$, $p<0.015$) and pessimism (Odds Ratio=2.32, $z=2.45$, $p=0.014$) were shown to make significant contributions to the risk for future suicidal acts (Likelihood Ratio test=14.8, $df=2$, $p<0.001$). In addition, the two factors were additive such that having high scores on either one of the factors increased risk to a similar degree. When both factors had high scores then the risk of suicidal acts in the two-year period was greater (Figura 5).

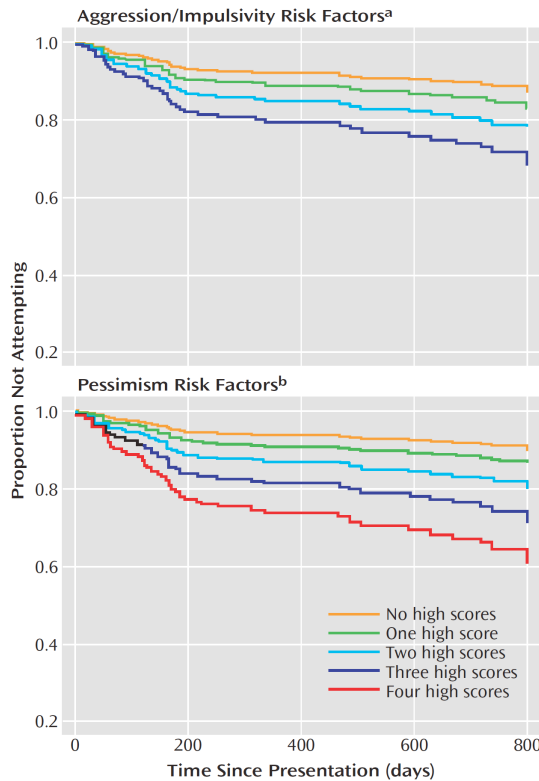
Figura 5. Additive effect of high scores on the aggression/impulsivity factor and the pessimism factor on future suicidal acts.



The measures constituting the aggression/impulsivity factor were the Brown-Goodwin Aggression Scale, Buss-Durkee Hostility Inventory, and Barratt Impulsivity Scale. The measures constituting the pessimism factor were the Beck Depression Inventory, Beck Hopelessness Scale, Scale for Suicide Ideation and Reasons for Living Inventory.

Finally, the presence of high scores on any of the given scales that contributed to the aggression/impulsivity factor or the pessimism factor also appeared to increased risk for suicidal acts (O.R.=1.34, $z=2.02$, $p=0.043$ and O.R.=1.38, $z=1.92$, $p=0.055$), although the aggregate pessimism factor did not quite reach statistical significance (Figura 7). Thus, the presence of a diathesis clearly increases risk for future suicidal acts.

Figure 6. Additive effects of obtaining high scores on each of the scales entered into the principal component analyses for the aggression/impulsivity factor (BGA, BDHI, BIS) and the pessimism factor (BDI, BHI, SSL, RFLS).



^a The measures constituting the aggression/impulsivity factor were the Brown-Goodwin Aggression Scale, Buss-Durkee Hostility Inventory, and Barratt Impulsivity Scale.

^b The measures constituting the pessimism factor were the Beck Depression Inventory, Beck Hopelessness Scale, Scale for Suicide Ideation, and Reasons for Living Inventory.

8.3 Sex Differences in Clinical Predictors of Suicidal Acts after a Major Depressive Episode in Affective Disordered Patients

8.3.1 Baseline Characteristics of Subjects

At the initial assessment, men and women did not differ in age, marital status, number of children, educational level, cigarette use, or family history of suicidal acts (Table 7). More depressed women than men had made suicide attempts (Table 8). However, they did not differ in suicidal ideation, suicidal intent, or severity of the medical damage caused by the most lethal attempt. Men and women had similar levels of impulsivity, hopelessness, hostility, reasons for living, psychiatric impairment, and frequency of early parental separation (Table 8).

Table 7. Baseline Demographic Characteristics of Men and Women in a Study of Suicidal Acts in the 2 Years Following a Major Depressive Episode.

	Men (N=130)	Women (N=184)	t (Chi ²)	p
Age (years)	37.51±12.71	37.80±11.37	-0.21	0.84
Education (years)	15.24±3.00	14.98±3.05	0.73	0.47
Number of children	1.1±1.5	1.0±1.3	0.53	0.60
Annual income (dollars)	26,822±33,191	18,215±20,704	1.85	0.06
Married	65(50.0%)	83(45.4%)	0.66	0.42
Cigarette smoker	55(43.0%)	66(36.1%)	1.51	0.22
Family history of suicidal acts	20(15.5%)	27(14.8%)	0.03	0.88

Table 8. Baseline Clinical Characteristics of Men and Women in a Study of Suicidal Acts in the 2 Years Following a Major Depressive Episode.

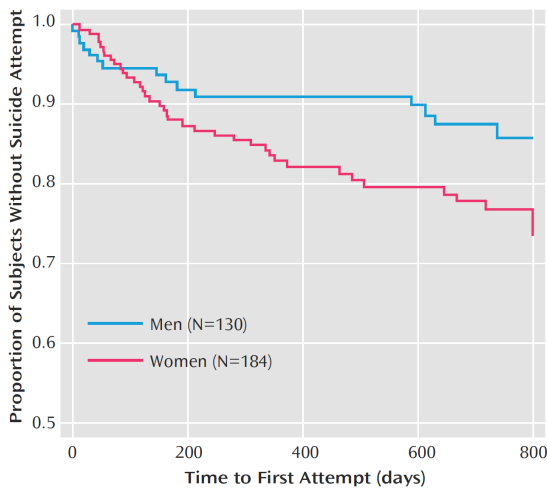
	Men (N=130)	Women (N=184)	t (Chi ²)	p
Previous suicide attempt	62 (47.7)	109 (59.2)	4.09	0.05
Borderline personality disorder	23 (18.8)	69 (38.8)	13.50	<0.001
Past alcohol or drug abuse	72 (55.8)	71 (38.8)	8.82	0.003
Early separation from either parent	33 (26.0)	65 (35.7)	3.27	0.07
Childhood history of abuse	32 (29.9)	81 (48.8)	9.57	0.002
Number of depressive episodes, excluding index episode	4.8±5.5	5.4±5.5	-1.66	0.10
Score on Scale for Suicide Ideation for 2 weeks before intake	13.03 ±10.42	14.41 ±10.58	-1.03	0.30
Number of previous suicide attempts	2.52 ±2.05	2.82 ±2.21	-0.91	0.36
Score on Lethality Rating Scale for most lethal attempt	3.61 ±2.22	3.28 ±1.96	1.02	0.31
Score on Suicide Intent Scale	16.86 ±5.88	15.55 ±5.84	1.42	0.16
Hamilton Depression Rating Scale	18.85 ±5.58	20.55 ±5.99	-2.55	0.02
Beck Depression Inventory	25.00 ±10.15	30.10 ±11.14	-3.96	<0.001
Beck Hopelessness Scale	11.64 ±5.84	12.60 ±5.75	-1.39	0.17
Reasons for Living Inventory	159.33 ±44.15	151.31 ±44.76	1.38	0.17
Brief Psychiatric Rating Scale	35.37 ±7.80	35.10 ±7.83	0.30	0.77
Brown-Goodwin Aggression Scale	19.87 ±6.14	17.42 ±5.02	3.82	<0.001
Buss-Durkee Hostility Inventory	39.29 ±11.86	34.60 ±11.52	1.75	0.09
Barratt Impulsivity Scale	52.18 ±17.46	51.55 ±16.67	0.29	0.77
Age at first major depressive episode (years)	27.1 ±13.1	23.9 ±12.6	2.19	0.03

A higher proportion of depressed men had past alcohol or drug abuse, and men reported more aggression than women. Women had higher rates of childhood abuse and comorbid borderline personality disorder, and they had earlier onsets of major depression and greater severity of both subjective and objective depression.

8.3.2 Follow-Up of Men and Women: Univariate Analyses

During the 2-year follow-up, four subjects completed suicide and 48 attempted suicide, representing 16.6% of the study group. Men and women were followed for similar periods of time, but women were more likely to attempt suicide than men in the follow-up period (hazard ratio=1.8, likelihood ratio $\chi^2=4.09$, $df=1$, $p<0.05$) (Figura 7).

Figura 7. Nonparametric Survival Curve Estimates of Suicidal Acts by Men and Women in the 2 Years Following a Major Depressive Episode^a.



^a Only the first 800 days are shown; the last recorded attempt was at 798 days.

For men, the odds of a future suicidal act were threefold greater if they had made a prior attempt; this increase fell short of statistical significance. Additionally, family history of suicidal acts increased the risk threefold. As hypothesized, drug use and cigarette smoking each more than tripled and quadrupled, respectively, the risk of suicidal acts during follow-up. Comorbid borderline personality disorder and early parental separation also increased the risk of suicidal acts (Tabla 9). There was a nonsignificant tendency of aggression, but not hostility, to predict future suicidal acts.

Tabla 9. Univariate Cox Proportional Hazards Regression Models Predicting Suicidal Acts by Men and Women in the 2 Years Following a Major Depressive Episode

	Men (n=130) HR (95% CI)	p	Women (n=184) HR (95% CI)	p
Age ^a	0.88 (0.70–1.10)	0.22	0.86 (0.71–0.99)	0.04
Previous suicide attempt	3.06 (0.97–9.60)	0.06	6.57 (2.33–18.60)	<0.001
Number of previous SA	1.18 (1.00–1.40)	0.05	1.39 (1.25–1.54)	<0.001
Scale Suicide Ideation ^a	1.28 (0.96–1.61)	0.09	1.28 (1.10–1.54)	0.002
Lethality Rating Scale score for most lethal attempt	1.02 (0.78–1.34)	0.89	1.26 (1.05–1.50)	0.01
Suicide Intent Scale for most lethal attempt ^a	1.34 (0.77–2.29)	0.32	1.34 (0.95–1.92)	0.07
Family history of suicidal acts	3.12 (1.06–9.13)	0.04	1.91 (0.87–4.20)	0.11
Childhood history of abuse	1.43 (0.36–5.74)	0.62	1.38 (0.68–2.77)	0.37
Separation from either parent	4.26 (1.45–12.49)	0.008	0.95 (0.49–1.86)	0.88
Alcohol abuse	1.84 (0.64–5.30)	0.26	1.24 (0.63–2.44)	0.53
Cigarette smoking	4.28 (1.36–13.48)	0.01	2.41 (1.25–4.65)	0.009
Past drug use	3.44 (1.15–10.28)	0.02	1.74 (0.87–3.46)	0.12
Borderline personality disorder	3.53 (1.25–9.96)	0.02	2.12 (1.10–4.09)	0.02
Age at first major depressive episode ^a	0.93 (0.75–1.16)	0.48	0.98 (0.96–1.01)	0.28
Number of major depressive episodes	0.94 (0.81–1.08)	0.36	0.98 (0.91–1.04)	0.49
Brown-Goodwin Aggression Scale ^a	1.40 (0.94–2.01)	0.09	1.34 (0.98–1.84)	0.07
Barrat Impulsivity Scale ^a	1.00 (0.85–1.21)	0.89	1.10 (0.99–1.22)	0.07
Beck Depression Inventory ^a	1.22 (0.92–1.54)	0.18	1.22 (1.05–1.47)	0.01
Beck Hopelessness Scale score ^a	0.91 (0.59–1.40)	0.66	1.22 (0.87–1.68)	0.24
Buss-Durkee Hostility Inventory ^a	1.16 (0.91–1.40)	0.26	1.28 (1.10–1.47)	0.03
Hamilton Depression Rating Scale ^a	1.47 (0.92–2.29)	0.11	1.05 (0.79–1.34)	0.80
Reasons for Living Inventory ^a	0.97 (0.90–1.05)	0.37	0.91 (0.87–0.95)	<0.0001

^a Hazard ratio calculated as change in risk for 5-point difference in value.

Although we hypothesized that depressed women with previous suicide attempts would have a greater risk for future suicidal acts, we did not anticipate the magnitude of this effect: a sixfold increase. Moreover, each prior attempt increased the risk of a future suicidal act by one-third. Suicidal ideation and lethality of past attempts also increased the risk of future suicidal acts for women (Tabla 9). As hypothesized, greater subjective depression, fewer perceived reasons for living, and borderline personality disorder also increased the risk of a suicide attempt during follow-up. Like men, female cigarette smokers were at greater risk for suicidal acts. Contrary to our prediction, hostility was a significant risk factor in women; aggression and impulsivity tended to increase risk as well.

8.3.3 Follow-Up of Men and Women: Multivariate Analyses

When all significant predictors of suicidal acts for men identified by univariate analyses (Tabla 9) were evaluated together, cigarette smoking and family history of suicidal acts emerged as the most robust predictors of future suicidal acts (Table 10), but early separation from family, borderline personality disorder, and past drug abuse were no longer predictive.

Tabla 10. Multivariate Cox Proportional Hazards Regression Model Predicting Suicidal Acts by Men and Women in the 2 Years Following a Major Depressive Episode

	Hazard Ratio Men (N=130)	p	Hazard Ratio Women (N=184)	p
At least one previous suicide attempt	1.62	0.47	4.98	0.04
Suicide Ideation score ^b	— ^a	— ^a	1.06	0.03
Family history of suicidal acts	3.22	0.05	— ^a	— ^a
Early separation from either parent	2.24	0.17	— ^a	— ^a
Cigarette smoking	4.21	0.04	2.87	0.02
Past drug use	1.08	0.91	— ^a	— ^a
Borderline personality disorder	3.02	0.09	1.62	0.26
Beck Depression Inventory score ^b	— ^a	— ^a	1.16	0.25
Buss-Durkee Hostility Inventory score ^b	— ^a	— ^a	1.16	0.14
Reasons for Living Inventory score ^b	— ^a	— ^a	0.95	0.13

^a Variable was not significant in univariate model.

^b Hazard ratio calculated as change in risk for 5-point difference in score.

Upon exploring reasons for the decreased effect of drug abuse on future suicidal acts, we found associations between drug abuse in men and smoking (71.1% of men with past drug abuse also smoked, $p < 0.0001$), borderline personality disorder ($p < 0.0001$), early parental separation ($p < 0.003$), and past suicide attempts ($p < 0.03$). In fact, the association between past drug abuse and smoking accounted for most of the predictive power of drug abuse among men (hazard ratio for drug abuse adjusted for smoking history=2.15, $p < 0.22$); the rest of the effect of drug abuse on future risk was accounted for by the other aforementioned variables.

For women, the multivariate analyses revealed that previous attempts, suicidal ideation, and smoking had independent effects on the risk for suicidal acts (Tabla 10). The presence of multiple suicide attempts, borderline personality disorder, greater subjective depression, fewer perceived reasons for living, and hostility were no longer significant. The effect of borderline personality disorder on future risk found in the univariate analyses was due to its close association with past attempts (hazard ratio for borderline personality disorder adjusted for previous attempt=1.35, $p < 0.39$). Most of the depressed women with borderline personality disorder (81.2%) had past suicide attempts. However, we were unable to demonstrate the effects of hostility in the multivariate analysis, probably because of limitations in statistical power. The predictive power of hostility was not explained by its association with previous attempt history, borderline personality disorder, or any other variable from the model, despite hostility's significant association with both borderline personality disorder and previous suicide attempts. Instead, the hazard ratio for hostility in the multivariate model was close to that from the univariate analysis, but the statistical significance of its predictive power decreased as more variables were added, ultimately resulting in a nonsignificant effect. This statistical limitation also appeared to be at work in the case of reasons for living.

8.4 Adequacy of Antidepressant Treatment

The follow-up rates were 84% at 3 months (N=114), 76% at 12 months (N=104), and 64% at 24 months (N=87). Twentyone (15%) of the 136 subjects attempted suicide during the follow-up period. None of the attempts was fatal. More than 50% of the attempts occurred within 5 months of discharge. For the attempters, the median time from hospital discharge until a suicidal act was 132 days (mean=185.1, SD=191.2, range=14–704 days) (Figura 8).

The first model, which included age, sex, lifetime number of suicide attempts at baseline, and interaction between age and number of suicide attempts, showed significant predictive power for suicide attempts during the follow-up period (Tabla 11). For each lifetime suicide attempt at baseline, the risk of suicide attempts in the follow-up period increased by about 30%; the 95% confidence interval (CI) was 16% to 48%. For each year of age, the risk of a suicide attempt in the future decreased. Thus, older patients were less likely to reattempt suicide than were younger patients who had made the same number of previous suicide attempts.

Figura 8. Estimated Survival Curve Indicating Number of Days Between Hospital Discharge and First Suicide Attempt for 136 Patients With Major Depression

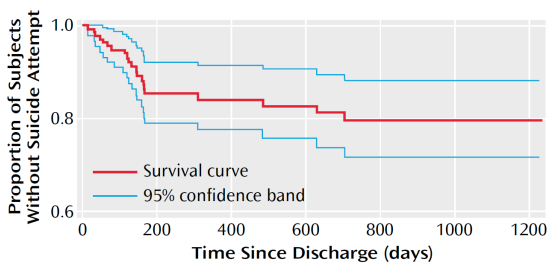


Tabla 11. Relation of Baseline Characteristics to Time Between Hospital Discharge and First Suicide Attempt for 136 Patients With Major Depression. Relation to Suicide Attempts During Follow-Up, From Cox Proportional Hazards Analysis (* Mean-centered variable).

	Hazard Standard	Robust Ratio Error	z	p
Sex	0.98	0.26	-0.09	0.93
Age*	0.94	0.03	-2.34	0.02
Number of lifetime suicide attempts *	1.31	0.06	4.25	0.00002
Interaction of age and number of suicide attempts	1.01	0.01	1.21	0.23

In the second model (Tabla 12), the risk of a suicide attempt was 7.23 times as high (95% CI=1.7–30.9) for patients who experienced a major depressive episode in the follow-up period. Previous suicide attempts were a significant predictor and increased the risk of an attempt during follow-up in this model also. We found no relationship between the adequacy of antidepressant treatment during the follow-up period and the risk of making a suicide attempt in the 2 years after discharge (Tabla 12). However, antidepressant treatment during the follow-up period was rated inadequate both during most epochs and on average for the total study group

(mean rating=2.1, SD=1.4). Moreover, 18 patients (13%) received no psychopharmacologic treatment during the entire follow-up period. Of those who were treated, the mean rating for treatment was 2.5 (SD=1.2, median=2.5), below the minimum for adequate treatment. Following are examples of mean daily antidepressant doses, in milligrams: desipramine, 177.0 (SD=93.3); bupropion, 284.8 (SD= 122.9); fluoxetine, 32.9 (SD=19.2); sertraline, 120.7 (SD=49.8); paroxetine, 42.5 (SD=19.4); nefazodone, 175.0 (SD=35.4); citalopram, 38.3 (SD=20.4); mirtazapine, 88.1 (SD=87.5); and phenelzine, 45.0 (SD=22.5). One subject received 200 mg/day of fluvoxamine. Nine (43%) of the 21 subjects who attempted suicide were receiving adequate antidepressant treatment (i.e., had scores of 3 or higher on the Antidepressant Treatment History Form).

Tabla 12. Relation of Age, Previous Suicide Attempts, and Follow-Up Characteristics to Time Between Hospital Discharge and First Suicide Attempt in 136 Subjects With Major Depression. Relation to Suicide Attempts During Follow-Up, From Cox Proportional Hazards Analysis (* Mean-centered variable).

	Hazard Standard	Robust Ratio Error	z	p
During follow-up period				
• Adequacy of antidepressant treatment	1.11	0.25	0.40	0.69
• Presence of major depression	7.23	0.74	2.67	0.008
• Interaction of treatment intensity and presence of major depression	0.67	0.25	-1.51	0.13
At hospital admission				
• Age	0.95	0.03	-1.89	0.06
• Number of lifetime suicide attempts*	1.53	0.09	4.61	0.000004
• Interaction of number of suicide attempts and age	1.00	0.26	1.10	0.27

Tabla 13. Adequacy of Antidepressant Treatment During Follow-Up for Patients Hospitalized for Major Depression With and Without Previous Suicide Attempts. Score for Adequacy of Treatment (range=0–5; adequate= ≥ 3)

Time Period	Previous Attempts (N=62)		No Previous Attempts (N=48)		t	p
	M	SD	M	SD		
Entire follow-up	1.9	1.5	2.4	1.2	-1.86	0.07
Periods of major depression	1.9	1.4	2.3	1.5	-1.12	0.27
Periods without major depression	1.5	1.5	2.6	1.3	-2.57	0.01

Subjects with a history of suicide attempts at baseline were not treated more vigorously during follow-up than nonattempters (Tabla 13). Furthermore, during periods of major depression the subjects with a history of suicide attempts at baseline were not treated more vigorously during follow-up than nonattempters (Table 13). The presence or absence of comorbid borderline personality disorder was not related to the adequacy of antidepressant treatment; the mean rating of adequacy of treatment was 2.1 (SD=1.5) for subjects with borderline personality disorder and 2.2 (SD=1.4) for those without it ($t=-0.39$, $df=104$, $p=0.70$). When we added borderline personality disorder as a predictor in the survival analysis that included age, sex, and number of previous suicide attempts, borderline personality disorder did not predict suicide attempts during the follow-up period (hazard ratio=1.35, SE=0.25, $p=0.23$).

8.5 Role of life events in precipitating suicidal behavior

8.5.1 Baseline Clinical Characteristics

At baseline, depressed subjects with history of suicide attempt (baseline attempters) were younger than those without a history of attempt (baseline nonattempters). Baseline attempters were also more likely to have suffered childhood abuse, and reported more past life events. They were more likely to have a history of past substance misuse and borderline personality disorders. They reported greater subjective depression; yet their clinician-assessed depression did not differ significantly from that of the baseline non-attempters. Also, they were more aggressive and hostile, gave fewer reasons for living and reported more suicidal ideation (Tabla 3).

8.5.2 Prospective Clinical Predictors

Prospective data covered 228,024 person-days grouped into 4,036 subject-epochs (intervals with constant RLCQ and MDE status, uninterrupted by a suicide attempt or follow-up visit), 9 epochs per subject on average, median length of 61 days (inter-quartile range [IQR]: 21-89 days). Subjects' median time in the study was 737 days (IQR: 416-806 days). 74 (1.8%) epochs ended in a suicide attempt. Forty (9.5%) subjects had at least one suicide attempt during follow-up: 25 subjects had one attempt, 7 had 2 attempts, and 8 had 3 or more attempts in that period. Almost all subjects (97.9%) reported at least one stressful life change and most (70.9%) had some epochs with MDE over the study period (Tabla 14). However, only 28.4% of person-days were characterized by an MDE, while 66.5% of person-days were part of an epoch with a RLC.

Tabla 14. Summary of Recent Life Changes Scale (N=430 subjects, n=228,024 person-days).

Stress	% subjects with stress during 2-year	% person-days with stress
Health	77.2	29.3
Work-related	84.9	23.9
Home and Family	76.7	28.6
Personal/Social	84.7	39.1
Financial	65.6	22.1
All kinds	97.9	66.5
	% subjects with MDE during 2-year	% person-days with MDE
MDE	70.9	28.4

A longitudinal Cox regression model which included the total score of life events from the RLCQ and the MDE indicator during the follow-up period, controlling for age, sex and aggression and pessimism factors predicted future suicide attempt during the follow-up period (Robust score test= 28.06, $df= 8$, $p=0.0004633$). Three variables were significant: current Major Depressive Episode, the second baseline pessimism factor, and being female (Tabla 15).

Tabla 15. Predicting Suicide Attempt Based on Stress

Variable	Stress (Total)		Health-related Stress (Total)	
	HR (95% CI)	p	HR (95% CI)	p
	4.90		4.73	
MDE	(2.52, 9.52)	<.0001	(2.73, 8.22)	<.0001
	1.02		1.35	
Stress	(0.94, 1.14)*	0.6503	(1.11, 1.73)*	0.0749
	1.14		1.13	
Aggression1	(0.74, 1.76)	0.5619	(0.88, 1.44)	0.3431
	1.12		1.12	
Aggression2	(0.82, 1.54)	0.4696	(0.88, 1.43)	0.3423
	1.22		1.22	
Pessimism1	(0.82, 1.80)	0.3236	(0.93, 1.60)	0.1481
	1.54		1.54	
Pessimism2	(1.05, 2.26)	0.0283	(1.16, 2.04)	0.0031
	0.98		0.98	
Age	(0.95, 1.00)	0.0761	(0.95, 1.00)	0.0550
	0.36		0.36	
Sex	(0.14, 0.90)	0.0294	(0.19, 0.67)	0.0012

* HR was reported for 50 point increase of the total score.

The life events score was not significant. The life events score did not predict suicide attempt in an unadjusted model (HR=1.02 per 50 point increase, 95% CI: 0.96-1.14, $p=0.4950$), either. The possibility of an interaction between MDE and life events score was also examined, but the interaction term was not significant (data not shown). When the stress score was tested by domain, the Health domain total score was a significant risk factor for suicide attempt (HR=1.42 for each 50 point increase, 95% CI: 1.01-1.91, $p<0.0326$), but did not remain significant after Bonferroni correction (Tabla 15),

and in the adjusted model the term lost significance altogether.

Tabla 16. Predicting Suicide Attempt Based on Stress

Variable	RLC31B (Total)		RLC8C (Total)	
	HR (95% CI)	p	HR (95% CI)	p
MDE	4.96 (2.55, 9.65)	<.0001	4.90 (2.82, 8.50)	<.0001
RLC Stress Item	7.61 (3.14, 18.43)	<.0001	5.25 (1.82, 15.08)	0.0022
Aggression1	1.13 (0.74, 1.72)	0.5668	1.17 (0.92, 1.50)	0.2034
Aggression2	1.14 (0.83, 1.55)	0.4250	1.13 (0.89, 1.44)	0.3060
Pessimism1	1.21 (0.81, 1.79)	0.3500	1.23 (0.94, 1.61)	0.1370
Pessimism2	1.56 (1.05, 2.31)	0.0277	1.59 (1.19, 2.12)	0.0017
Age	0.97 (0.95, 1.00)	0.0667	0.98 (0.95, 1.00)	0.0601
Sex	0.36 (0.14, 0.89)	0.0277	0.37 (0.20, 0.69)	0.0017

* HR was reported for 50 point increase of the total score.

In exploring which of the 76 life event items were associated with increased risk of future suicidal acts (using 1-sided tests for the stress variables), 2 were found to be significant in the multi-variable model after using the Benjamini-Hochberg adjustment with FDR=15%. These items were RLCQ item 31B: “a child leaving home to attend college” (ratio of epochs with attempt associated

with this stress: 1 /14, HR=7.61, 95% CI: 3.14-18.43, p<0.0001) and RLC item 8C: “had a change in your responsibilities at work: promotion” (attempt/stress: 4/58, HR=5.25, 95%CI: 1.82-15.08, p=0.0022) (Tabla 16). Five more items were significant at the 0.05 level before adjustment for multiple testing with hazard ratios ranging between 2.5 and 4.8, and for twenty-one additional items, the stressful event never occurred in the same epoch as an attempt, and the model did not converge.

9 DISCUSSION

Abstract

Los estudios prospectivos de seguimiento como el que se presenta son fundamentales para corroborar los factores de riesgo, los factores protectores y el efecto de los tratamientos sobre la conducta suicida. Estos estudios son muy costosos en tiempo y recursos y tienen el inconveniente de las pérdidas de sujetos durante el seguimiento (que pueden sesgarlo), y en el caso de sucesos infrecuentes -como afortunadamente es la muerte por suicidio- la necesidad de un amplio tamaño muestral (personas/año) para alcanzar un poder suficiente para testar las hipótesis.

En este trabajo se han podido comprobar todas las hipótesis excepto lo referente al papel precipitante de los acontecimientos vitales y el efecto protector del tratamiento antidepressivo. Sin duda todos estos hallazgos permitirán tratar mejor a los pacientes, identificar sus factores personales de riesgo, y poner más cuidado en la prescripción y monitorización de los fármacos.

9.1 Hypothesis contrast

9.1.1 Clinical Predictors of Suicidal Acts after a Major Depressive Episode in Affective Disordered patients

Our findings indicate that the three strongest predictors of suicidal acts in a two year follow up period are history of suicide attempt, subjective depression, and cigarette smoking. Each of these variables increased risk two to fourfold. Furthermore, the data support our model which posits that suicide attempters can be distinguished from non-attempters not by severity of illness, as measured by a clinician, but rather by a propensity to react with more subjective distress or pessimism to similar stressors and/or by displaying more aggressive/impulsive tendencies. The presence of both of these vulnerabilities appears to have additive effects on risk.

Past suicidal behavior as a predictor of future suicidal behavior: A history of suicide attempt increased the risk for future suicidal behavior more than four fold. These findings are consistent with those of Nordstrom et al. (1995) who reported that in mood disordered patients the suicide rate was 15% for recent attempters compared to 5% for patients without a current suicide attempt. Fawcett et al. (1990) reported that history of suicide attempt was prospectively associated with suicide completion in affective disordered patients. Similarly, other prospective studies have also shown that a history of suicide attempt increases the risk for subsequent attempts (Duggan y cols., 1991; Coryell y cols., 2002; Paykel & Dienelt, 1971; Dorpat & Ripley, 1967; Avery & Winokur, 1978; Wasserman & Cullberg, 1989; Brent y cols., 1993; Leon y cols., 1999). Thus, a history of suicide attempts predicts future suicidal acts in the relatively brief time frame of two years after a MDE.

Subjective Depressive Symptoms as a predictor of future suicidal behavior: Subjective severity of depression (BDI) predicted future suicidal acts in this study, as was the case in our retrospective study (Mann y cols., 1999b). Of note, in a ten-

year prospective study Beck et al. (1985) reported that only the pessimism item of the BDI was a significant predictor of suicide completion. This difference may be related to the fact that the outcome variable in Beck's study was suicide completion, whereas only four of the 42 suicidal acts in our sample were suicide completions.

We and others have shown that prior suicidal behavior does not appear to be related to objective severity of depression (Malone y cols., 1995a; Cornelius y cols., 1995; van Praag & Plutchik, 1984) as rated by observable symptoms and measured by instruments such as the Hamilton Rating Scale. These counterintuitive findings may explain why clinicians have difficulty in identifying those at risk (Mann y cols., 1999b) since clinically rated psychopathology (HDRS, BPRS, SANS, SAPS) is not related to future suicidal behavior. Evaluating cognitive or subjective reports of severity of depression, hopelessness, and perceived reasons for living, might better indicate to clinicians the level of risk for suicidal behavior.

Cigarette smoking as a predictor of future suicidal behavior: Being a cigarette smoker increased the risk of eventual suicidal acts in this sample more than two fold. A prospective study of army recruits (Angst & Clayton, 1998) also showed that those who committed suicide were twice as likely to be smokers (82%), compared with those dying from accidents (40%) or controls (40%). Angst and Clayton (1998) have suggested that cigarette smokers are more likely to suffer from MDE, antisocial personality disorder, and borderline personality disorder. All of the subjects in our sample were depressed, and in this study smoking was not associated with the presence of Cluster B PD but rather with alcohol and substance abuse. Substance abuse disorders are reported to increase risk for eventual suicidal behaviors (Statham y cols., 1998; Beck y cols., 1989) and this effect may be mediated either through pharmacologically induced disinhibition, depletion of monoamines, or due to a common diathesis or relevant psychopathology such as aggression/impulsivity. Perhaps some of the

predictive power of cigarette smoking stems from its association with these other risk factors. Indeed, we have shown that cigarette smokers have lower serotonergic functioning than nonsmokers (Malone y cols., 2003) and more aggressive/impulsive traits (Meulemans y cols., 1992; Phillips, 1992; Tanskanen y cols., 1998).

Diathesis and Future Suicidal Behavior: Our results support the notion that suicidal behavior is not merely a response to a stressor. Instead, a diathesis must be present, placing the individual at higher risk for suicidal acts. This diathesis, characterized by a tendency for pessimism in the context of a stressor and/or pronounced aggressive/impulsive traits, increases the risk for future suicidal acts. Moreover, the effect of the aggression/impulsivity factors and pessimism factors was additive from two vantage points. There is added risk conveyed by high scores on each of the scales that went into the factors as well as additive risk conveyed by attaining high scores on both of the factors themselves. This suggests that each of the factors as well as their components contribute to future suicidal acts, underscoring the dimensionality of the diathesis.

Pessimism in the prediction of suicidal behavior: As hypothesized the pessimism factor generated from the BDI, BHS, SSI, and RFLI predicted suicidal acts in the follow up period. This is consistent with other prospective investigations (Fawcett y cols., 1990; Beck y cols., 1985) in which more pronounced suicidal ideation is reported to increase the risk of future acts. The presence of suicidal ideation with highly developed plans has been associated with risk of suicidal acts in epidemiologic samples as well (Kessler y cols., 1999). The current study suggests that in addition to serving as a marker for imminent suicidal acts, as reflected in the clinical practice of hospitalizing or increasing the frequency of monitoring in cases with pronounced suicidal ideation, the presence of suicidal ideation indicates longer term risk as well.

Fewer perceived reasons for living in the context of an acute MDE were also considered part of pessimism. In this sample, baseline suicide attempters and nonattempters did not differ at baseline in terms of number of children, marital status, and employment, factors postulated to protect individuals. However, attempters had lower scores on the RFLI and perceived reasons for living appeared unrelated to objective recent life events or signs of connection to others (Malone y cols., 2000). This first prospective study of the RFLI confirms that its negative association with a history of suicidal acts extends to their future occurrence.

Our current finding supports the notion that hopelessness has some predictive power for eventual suicidal acts. However, the literature is

inconsistent. Hopelessness has been reported to be a predictor of suicide completion in the long term (2 to 10 years) but not in the short term (Fawcett y cols., 1990). Yet, another prospective study of suicide attempters which followed subjects for 5-10 years, found that BHS was not significantly associated with eventual suicide, even though an earlier ten-year prospective study by the same group had indeed found that hopelessness was the only scale differentiating suicidal ideators who later committed suicide from ideators who did not (Beck y cols., 1989). A recent 5-year prospective study of patients with Major Depression showed that severe hopelessness at index assessment was associated with suicide completion in the follow up period (Schneider y cols., 2001). Additionally, hopelessness has been reported to be the most significant predictor of repeated parasuicide in non-psychotic parasuicide attempters (Sidley y cols., 1999). Some of these discrepancies may be attributable to differences in patient samples. Our study did not show hopelessness to be an independent predictor in the multivariate analysis, but the pessimism component suggests that it has a role in prediction. Whether it is more useful in the prediction of suicide completion and not attempts, or is predictive of suicidal behavior beyond two years is still unknown.

We suggest that combining each of these scores into one factor may be a more robust way of ascertaining future suicide risk, since the development of subjective distress in the face of a stressor such as a MDE is likely to have multiple dimensions including hopelessness, cognitive experience of depression, and a perception of fewer reasons for living, as well as suicidal ideation. In addition, these results support the use of various measures of depression and despair in studies of suicidal behavior.

Impulsive and Aggressive Traits: The component generated from the aggression/impulsivity scales (BIS, BGA and BDHI) was a significant predictor of future suicidal acts. Impulsivity has been associated with a history of suicide attempt in psychiatric patients in retrospective studies (Mann y cols., 1999b; Apter y cols., 1993; Horesh y cols., 1999; Oquendo & Mann, 2000; Plutchik & van Praag, 1997). The current study supports the notion that impulsivity contributes to risk of future suicidal behavior as well. Only two prospective studies have considered impulsivity, one finding that as one of a cluster of factors it contributed to long term suicide risk (Maser y cols., 2002), and the other reporting that it predicted only attempts, not completions (Pokorny, 1983). Impulsivity may influence the likelihood of suicidal acts but is likely to have a more complex effect on lethality of suicidal attempts. We have reported that suicide attempters who require medical hospitalization for

treatment of the sequelae of their attempt are less impulsive than attempters with less lethal behavior (Oquendo y cols., 2003a). Similarly, Baca Garcia et al. (2001) have reported that those who plan their attempt over a longer period of time tend to make more severe attempts. It seems likely that impulsivity increases the risk of future suicidal acts but diminishes the planning required to inflict more severe medical damage.

Although suicide attempters have been documented to be more aggressive than non-attempters in samples with personality disorders (Coccaro y cols., 1989; Corbitt y cols., 1996), unipolar depression (Malone y cols., 1995a), bipolar disorder (Oquendo y cols., 2000), and criminals (Linnoila y cols., 1983), the relationship between aggression and the prediction of suicidal acts has been examined in only one other prospective study. Consistent with our finding that aggressive behavior increases the risk of suicide attempts in the follow up period, Angst and Clayton (1998) reported that army recruits who later died by suicide or accident were more aggressive than controls. The presence of anger at oneself predicted future suicidal ideation in a group of male students followed for 8 years (Goldney y cols., 1997), perhaps an early sign of increased risk for future suicidal acts. Thus the aggressive/impulsive dimension appears clearly linked to both past and future suicidal behavior.

9.1.2 Sex Differences in Clinical Predictors of Suicidal Acts after a Major Depressive Episode in Affective Disordered Patients

A previous suicide attempt is a powerful predictor of future suicidal acts (Oquendo y cols., 2004b; Leon y cols., 1999). In this study, men with past suicidal behavior had a threefold, but nonsignificantly, greater risk for future attempts. Women had a significant, sixfold higher risk of a future suicide attempt if they had made past attempts. The large effect among depressed women may be due to the earlier onset of depression among women, perhaps hampering the development of coping skills and rendering them more vulnerable to suicidal behavior. Alternatively, because men often use more lethal means than women, they may be more likely to die as a consequence of suicidal behavior, thus skewing clinical groups toward men with fewer, less lethal attempts.

9.1.2.1 Risk Factors for Men

Substance abuse has been reported to predict suicide attempts and completed suicide by people with mood disorders in general (Maser y cols., 2002). In this study group, past drug abuse predicted suicidal behavior in men only, a finding that is consistent with the observation that suicide deaths among men frequently occur within the

context of substance use disorders (Rich y cols., 1988). Drug and alcohol misuse may predispose men to suicidal behavior in the setting of disruptions in important relationships (Rich y cols., 1988). Whether disinhibition (Mann y cols., 1999b), serotonergic dysfunction (Mann y cols., 1999b) due to drug abuse, interpersonal factors, or a combination of these mediate the effect of drug abuse on future risk in men requires further study. We expected aggression and hostility to affect future suicidal behavior in men. Our data suggest a 7% increase in risk for future suicidal acts for each point on the aggression scale, but the finding did not reach significance, nor did hostility predict suicidal acts. Although in this group, men reported more aggressive behavior than women, perhaps more aggressive depressed men at risk for suicidal acts do not seek treatment. We do not have data to address this possibility. Nonetheless, it has been noted that anger at oneself predicts suicidal ideation, not acts, in young men living in the community (Goldney y cols., 1997). The relationship between anger at oneself and aggression is likely to be complex.

Family history of suicidal acts tripled the risk of future suicidal acts only for the men in our study. Suicidal behaviors cluster in families (Brent y cols., 2002), independent of the transmission of psychiatric conditions (Egeland & Susse, 1985). A large epidemiologic study (Qin y cols., 2003) showed that a family history of psychiatric disorders increased the risk for suicide completion in both sexes, but it indicated a more robust effect of familial suicide on females than males. Whether family history affects males and females differently is unknown but could be related to genetic contributions from X-linked genes or mitochondrial DNA or differences in child rearing between the sexes. Moreover, the heritability of suicide attempts and completions in the two sexes may differ, resulting in these apparently contradictory results.

For men, early parental separation increased the risk of suicidal acts more than threefold. Early parental loss is a risk factor for suicide in adolescents and young adults regardless of sex (Andrews & Lewinsohn, 1992; Benjaminsen y cols., 1990). One retrospective study (Duggan y cols., 1991) demonstrated that early loss, separation, or inadequate child rearing in young men was more strongly associated with death by suicide than with death from car accidents. Differential effects by sex may relate to genetic or rearing differences; perhaps girls can attach to new caretakers more easily in the absence of a parent.

Multivariate analyses uncovered that among depressed men the predictive power of several of the variables could be explained by their relationship to the increased risk ascribable to

cigarette smoking. This finding underscores the need for studies that have comprehensive clinical assessments so that such relationships can be uncovered, leading to accurate predictive models for suicidal behavior.

9.1.2.2 Risk Factors for Women

We hypothesized that women with more subjective depression, fewer perceived reasons for living, borderline personality disorder, or a history of childhood abuse would be more likely to engage in future suicidal behavior. Except for childhood abuse, these factors were predictive in univariate analyses. Each point increase on the BDI increased the risk for suicidal acts in women by 4%. We previously reported that subjective depression severity is a risk factor for suicidal acts (Oquendo y cols., 2004b). Several studies have examined the predictive capacity of depressive subtype (Grunebaum y cols., 2004; Brodaty y cols., 1997; Lehmann y cols., 1988; Thornicroft & Sartorius, 1993), but none has focused on sex differences. The 1993 National Mortality Followback Survey (Kung y cols., 2003) found that, compared to women with natural deaths, women who completed suicide had endorsed depressive symptoms at all ages; however, depression was only a factor among older male suicide victims, implying that other conditions, such as alcoholism or substance abuse, are associated with suicide in younger men, such as those included in our study group (mean age=38 years) and that depression as a risk factor for suicide by men appears later in life.

There was an inverse relationship between risk for suicidal behavior and scores on the Reasons for Living Inventory for women. Women may attach more importance to their responsibilities toward children, an important factor assessed by the Reasons for Living Inventory. Studies show that being married is protective for men, whereas having a child under the age of 2 is protective for women (Qin y cols., 2000, 2003; Young y cols., 1994). Among women, the protective effect of marriage against suicide has been attributed to the effect of having children (Qin y cols., 2000; Durkheim, 1951).

For women, the number of previous suicide attempts, suicidal ideation, lethality of prior attempts, and hostility all increased the risk for suicidal acts. Each previous suicide attempt increased the risk of subsequent attempts by over 30%. These findings are consistent with the findings from two prospective studies, in which women who committed suicide had previously attempted suicide but men had not (Berglund & Nilsson, 1987; Bradvik & Berglund, 1993). Indeed, despite the similarity between men and women in the levels of suicidal intent, women's use of less lethal means may result in more frequent survival of attempts.

Several (Angst & Clayton, 1998; Fawcett y cols., 1987; Schneider y cols., 2001), but not all (Gladstone y cols., 2001; Oquendo y cols., 2004b), prospective studies have implicated suicidal ideation as a risk factor for future suicidal acts. Some cross-sectional studies showed greater suicidal ideation in female teens (Allison y cols., 2001; Rich y cols., 1992), while others showed no sex differences in suicidal ideation, despite higher prevalences of suicidal behavior in women, younger persons, those living alone, and women in urban areas (Renberg, 2001). Thus, the predictive capacity of suicidal ideation requires further study.

We found that in women, for each increment in medical damage from the most lethal attempt, future suicidal risk increased by 26%, suggesting that lethality and frequency of suicidal behavior are related in women. This is of concern in light of reports that the proportions of men and women who make medically serious suicide attempts are similar despite the fact that twice as many women use nonlethal methods (Beautrais y cols., 1996). Examining the medical consequences of attempts made by women may help guide assessment of risk for future suicidal acts.

For women, greater hostility increased the risk for a suicidal act. Hostility in association with depression has been linked to suicidal behavior (Mann y cols., 1999b; Weissman y cols., 1973) although why it should be predictive for women only is not clear. As mentioned previously, it is possible that more aggressive, hostile men at risk are not represented in clinical samples.

As was the case among men, multivariate analyses revealed that some of the predictive variables found in the univariate analyses owed their robustness to their association with other variables. Among women, past suicidal behavior explained the effect of borderline personality disorder on the future risk of suicidal acts. The complexity of finding appropriate predictors for rare events cannot be overstated.

9.1.2.3 Risk Factors Affecting Men and Women

We predicted that borderline personality disorder would increase the risk for suicidal acts in women. However, it also increased the risk for depressed men. Men and women with both major depression and borderline personality disorder have more suicide attempts and objective planning than do those with either diagnosis alone (Soloff y cols., 2000). This was the case for the subjects in this study: 81% of the patients with borderline personality disorder had previous attempts. Among the female subjects, a history of suicide attempts accounted for the predictive power of borderline personality disorder. However, for men, the predictive power of borderline personality disorder was only partially

explained by previous attempts. An association between “sensitive/brittle” personality and later suicide in depressed men but not women has been reported (Berglund & Nilsson, 1987; Bradvik & Berglund, 1993). Brittleness and sensitivity are perhaps more typical of narcissistic personality disorder but may also be consistent with borderline personality disorder. Although borderline personality disorder is less often diagnosed in men, its presence alongside depression may pose incremental risk for future suicidal behavior.

The only other risk factor that significantly predicted future suicidal behavior in both sexes was cigarette smoking. Cigarette smoking increases the risk for suicidal acts (Angst & Clayton, 1998; Oquendo y cols., 2004b; Tanskanen y cols., 1998) independent of the effects of major depression, alcohol abuse, or drug use (Breslau y cols., 2005), and smokers are reported to have more aggressive or impulsive behaviors. Current smokers but not former smokers (Whitfield y cols., 2000) have lower monoamine oxidase activity, which may result in serotonergic dysregulation, mediating the association of cigarette smoking with depression and suicide (Mann y cols., 1999b).

9.1.3 Adequacy of Antidepressant Treatment

Relapse or recurrence of major depression increased the risk of suicide attempt during the 2 years after discharge from the hospital, underlining the importance of optimal maintenance antidepressant treatment as a suicide prevention strategy. We were unable to demonstrate that pharmacotherapy of major depression protected patients against suicide attempts in this naturalistic prospective study. One explanation is the overall undertreatment of depression, which undermines the statistical power to measure the benefit of treatment. We found that nine (43%) of the 21 follow-up suicide attempts occurred while patients were receiving adequate treatment. Of those 21 patients, four were depressed at the time of their attempts despite adequate treatment, suggesting that treatment resistance is important. However, little attention has been given in the literature to the role of treatment-resistant depression in suicidal behavior (Oquendo y cols., 1997). The significance of the inadequacy of the treatment in this study is heightened by the fact that 54% of our inpatient group reported having made a suicide attempt before study entry and thus were at high risk for future suicide attempts. Nonetheless, the suicide attempters were not treated more aggressively than nonattempters. The undertreatment was not explained by the presence of borderline personality disorder, which could have caused diagnostic complications. The

presence of borderline personality disorder had no effect on treatment adequacy. Moreover, in the previous attempters, the appearance of a major depressive episode during follow-up did not trigger more intense pharmacologic treatment.

The small number of suicide attempts during follow-up and possible confounds, such as psychotherapy received during follow-up, may have hampered detection of an effect of antidepressant treatment on suicide attempt rates during the follow-up period. Studies directly examining the effects of antidepressant medication on suicidal behavior suggest a role for somatic treatments in the prevention of suicidal acts. In a meta-analysis by Montgomery et al. (1995), paroxetine reduced the frequency of completed suicide and suicidal thoughts more than did placebo or other active antidepressant treatment, but it did not reduce the number of suicide attempts. Similarly, in the National Institute of Mental Health collaborative depression study (N=643) there was 56% less risk for suicidal acts among patients taking fluoxetine than among patients receiving no somatic therapy, but this finding was not statistically significant, possibly because of clinical differences in illness severity and suicide history in the subjects treated with fluoxetine (Leon et al., 1999). In addition, of the subjects treated with fluoxetine, the proportion with suicidal behavior was significantly reduced from 38.9% before fluoxetine treatment to 3.8% during fluoxetine treatment. In contrast, Khan et al. (2000) recently reported a meta-analysis that showed that placebo and active antidepressant treatment did not differ in their effects on rates of suicide attempts and completions. However, they studied subjects entered into phase II or III trials for new antidepressants that were ultimately approved by the Food and Drug Administration, and the subjects were selected so as to exclude the comorbidity or acute suicidality often seen in clinical populations. The strongest evidence for psychopharmacologic protection against suicidal behavior comes from controlled and naturalistic treatment studies of lithium and suicidal behavior (Modestin & Schwarzenbach, 1992; Muller-Oerlinghausen y cols., 1992; Tondo y cols., 1998). These studies suggest that lithium has an antisuicidal effect independent of its mood-stabilizing properties. Because many of the aforementioned studies were carried out in lithium clinics, where blood serum lithium levels are routinely monitored and noncompliance easily identified, it is possible that part of the robustness of lithium’s antisuicidal properties is due to compliance and not necessarily specific to lithium.

At least one study has shown such an effect (Kallner y cols., 2000). In the current study, whether inadequate treatment was due to patients’

difficulties with compliance was not determined. Nonetheless, these studies support the notion that pharmacotherapy can have antisuicidal effects. Improved identification of major depression and more widespread prescription of antidepressant medications appear to be associated with declining rates of completed suicide as well. In Hungary and Sweden, suicide rates show a negative correlation with rates of treated depression (Rihmer y cols., 1990) and antidepressant prescription rates (Isacson y cols., 1996). The Gotland study (Rutz y cols., 1992) showed an increase in antidepressant prescription rates and a reduction of suicide rates after an educational program for general practitioners about the diagnosis and treatment of mood disorders. Conversely, lack of treatment of major depression has been associated with increased suicide risk. In Sweden, Isacson et al. (1996) reported that suicide risk among untreated depressed patients was 1.8 times higher than for those treated with antidepressants. In addition, postmortem studies have shown that major depression in suicide victims is infrequently diagnosed and ineffectively treated before death. Isacson et al. (1999) examined data from toxicological screens of 5,281 suicide victims in Sweden and detected antidepressants in only 12.4% of the men and 26.2% of the women. In the San Diego Study (Isacson y cols., 1994), half of the depressed suicide victims had consulted a physician in the 90 days before suicide, yet fewer than half of those were given prescriptions for antidepressants. Furthermore, toxicological tests revealed an absence of antidepressants in more than half of subjects for whom they were prescribed. Similarly, in Finland, Isometsä et al. (1994) found that although 45% of suicide victims with major depression were receiving psychiatric treatment at the time of death, only 6% had received antidepressants or electroconvulsive therapy in adequate doses.

This naturalistic prospective study of major depression and suicidal acts during a 2-year follow-up period after hospitalization for a major depressive episode showed clinically serious undertreatment of depression. This was so even for patients with a history of suicide attempts, who are at a higher risk for future suicidal acts. In fact, we found that for each lifetime suicide attempt at baseline, the risk of suicide attempts in the follow-up period increased by about 30%. Poor treatment of depression during follow-up has been reported (Keller y cols., 1982, 1986; Friedman y cols., 1992). In our previous retrospective study of patients seeking treatment at our center for major depression (Oquendo y cols., 1999), we found that they were strikingly undertreated, regardless of their past history of suicide attempts. The present prospective study

demonstrates a continuation of that practice of undertreatment after discharge from inpatient hospitalization for major depression, even for those at high risk for suicidal behavior. These findings are in agreement with the results of a study of 73 patients hospitalized after suicide attempts (Montgomery y cols., 1995). Using a similar statistical analytic technique but a different patient group, Leon et al. (1999) determined that for each additional prior suicide attempt, the risk of a suicide attempt in the follow-up period increased by 32%. Thus, both of these studies reveal that the hazard for suicidal acts in the follow-up period increases as a function of the number of suicide attempts before the index hospitalization, and they indicate that clinicians should obtain this information to assess risk (Sidley y cols., 1999). We have also confirmed our retrospective finding that suicide attempters and nonattempters are undertreated (Oquendo y cols., 1999).

A major depressive episode during the follow-up period emerges as the most robust predictor of suicide attempts in our study and emphasizes the need for better diagnosis and treatment of major depression.

9.1.4 Role of Life Events in Precipitating Suicidal Behavior

In this prospective study of patients in a major depressive episode (MDE) and meeting criteria for major depressive disorder (MDD) or bipolar disorder (BD), we evaluated selected baseline characteristics associated with suicide attempt history and assessed the predictive capacity of recent stressful life events on suicidal behaviors over the two-year follow-up period. Contrary to our hypothesis and clinical lore, but consistently with some prior studies (Lewinsohn, Rohde et al. 1994; Holma, Melartin et al. 2010; Spijker, de Graaf et al. 2010), we did not find evidence that life events served to precipitate suicide attempts. However, we did find some signals in secondary analyses. The health related concerns subscale, the “promotion at work” item and the “child leaving home to attend college” item did appear to increase risk, although the first did not remain significant after adjustment for multiple comparisons.

9.1.4.1 Positive and Negative Stressors

One possible interpretation is that the total score on the RLCQ is not the ideal way to assess the effects of stress because it includes both positive and negative stressors. However, as Rahe and others have argued, it is difficult to determine a priori whether an event will be perceived as positive or negative by a specific individual (Rahe 1978). In support of this, of the individual items from the RLCQ that appeared to increase risk for suicide attempt, one could be viewed as positive (eg a promotion at work) and the other as mixed

(child leaving home to attend college). One model of stress and coping proposes that in response to stressful events, individuals appraise both the threat value of the event and his/her capacity to respond to it (Lazarus 1984). Thus, appraisals vary based on past experience, personality traits, and perceived self-efficacy (Lazarus 1984) (Lazarus 1993; Bandura 1997). In support of this view, Johnson et al. (Johnson, Gooding et al. 2009) reported that positive self-appraisal moderated the association between stressful life events and suicidality, suggesting such positive self-appraisal confers resilience. Given that pessimism predicted suicide attempts in this sample, it may be that seemingly positive life events such as a job promotion may increase risk for suicidal behaviors due to negative self-appraisal and/or pessimistic feelings about the ability to perform in the new role. Since self-appraisal and perceived self-efficacy are potentially malleable factors through psychotherapies aimed at emotional regulation, this suggests a potential target for research on suicide risk reduction. Thus, even when life changes are seemingly positive, psychotherapeutic on improving self-appraisal, self-efficacy and application of emotional regulation techniques may be of utility as a possible preventative strategy, particularly in individuals with high pessimism scores.

9.1.4.2 Type of Stressors: Health Related Stressors as Precipitants

The Health Related domain on the RLCS has six items that include: major (in bed ≥ 1 wk or hospitalized) and minor injury or illness; major dental work; major change in eating habits; major change in sleeping habits; and major change in usual type and/or amount of recreation. That health related stressors were no longer significant after adjustment for current MDE suggests that the risk effect of health stress may be partially mediated by depression. Alternatively, it may be that some of the items listed on the Health Related Domain of the RLCS may be picking up neurophysiological changes caused by depression (i.e.: major change in eating habits; major change in sleeping habits; and major change in usual type and/or amount of recreation). Lewinsohn et al. (Lewinsohn, Rohde et al. 1994) also observed that health stressors were no longer significant in predicting suicide attempts after controlling for concurrent depression. Of note, and consistent with our prior reports based on sub-samples of the current subject group, we found that being female, having MDE recurrence, and one of the two baseline pessimism factors predicted suicidal attempts.

One prospective study that examined such associations in personality disordered individuals (Yen, Pagano et al. 2005), noted that negative

events pertaining to love/marriage and crime/legal issues were especially important, but health-related life events were not significant in the final model controlling for MDD and other factors. Borg & Stahl (Borg and Stahl 1982) observed that physical illness stressors were actually more common among controls than among suicide completers.

Most of the prospective studies analyzing life events and suicidal behaviors did not provide information regarding the type of life event (McKeown, Garrison et al. 1998; Caspi, Sugden et al. 2003; ten Have, de Graaf et al. 2009; Spijker, de Graaf et al. 2010).

9.1.4.3 The Predictive Capacity of Baseline Pessimism and Aggression/Impulsivity Factors

A surprising result is that, although we have previously reported in a subsample of this cohort that pessimism and aggression predict future suicidal behavior, in this analysis, the findings were somewhat different. After taking into account the occurrence of stressors and MDEs in the follow-up period, as well as baseline pessimism and sex, the aggression/impulsivity factor was not predictive. It is possible that much of the variance explained by the aggression/impulsivity is tied to MDE recurrence. Perhaps more aggressive and impulsive individuals suffer more MDEs as a consequence of their behaviors. McKeown et al. (McKeown, Garrison et al. 1998) observed that impulsivity at baseline was a significant predictor of suicide plans but not of attempts.

Lewinsohn et al. (Lewinsohn, Rohde et al. 1994) found that pessimism predicted future suicide attempt after controlling for depression, but pessimism lost significance in a multivariate model including other demographic and psychosocial factors.

Unfortunately, many of the prospective studies analyzing predictors of suicidal behaviors did not include measures of impulsivity and aggression (Lewinsohn, Rohde et al. 1994; Caspi, Sugden et al. 2003; Neeleman, de Graaf et al. 2004; Yen, Pagano et al. 2005; ten Have, de Graaf et al. 2009; Spijker, de Graaf et al. 2010).

9.2 Relevance

9.2.1 Clinical Predictors of Suicidal Acts After a Major Depressive Episode in Affective Disordered Patients

We found that the three most powerful predictors of future suicidal acts were a history of suicide attempt, severe subjective depression, and cigarette smoking, with each of these risk factors having an additive effect on future risk. Similarly, factor analyses revealed that a tendency towards pessimism and the presence of aggressive impulsive traits increased future risk. These findings suggest that in addition to obtaining a

history of suicidal behavior, assessment of subjective depressive severity, hopelessness and fewer perceived reasons for living, comorbidity with substance abuse disorders including nicotine, and personality factors such as Cluster B PD, impulsivity, and aggression, will assist the clinician in the identification of patients at higher risk so that they can be monitored more closely. Interventions including pharmacotherapeutic prophylaxis to prevent relapse or recurrence of depressive symptomatology or psychotherapeutic interventions targeting pessimism may protect at risk individuals from future suicidal behavior.

9.2.2 Sex Differences in Clinical Predictors of Suicidal Acts After a Major Depressive Episode in Affective Disordered Patients

From a clinical standpoint, the relative lack of protection afforded by reasons for living in men, compared to women, is notable. Furthermore, despite the well-documented fact that men are at greater risk for completed suicide, depressed female suicide attempters appear at relatively greater risk for repeated suicidal behavior. Thus, clinical evaluation may be enhanced by considering the difference between the sexes in the importance of risk factors for suicidal acts.

9.2.3 Adequacy of Antidepressant Treatment

A major depressive episode during the follow-up period emerges as the most robust predictor of suicide attempts in our study and emphasizes the need for better diagnosis and treatment of major depression. The efficacy of educational programs should be tested, targeting not only general practitioners but also psychiatrists, other medical specialists, and primary care physicians.

Future studies of antidepressants and their effects on suicidal acts should also include controlled treatment for high-risk patients, with monitoring of blood levels (where appropriate), so that the adequacy of antidepressant prescriptions can be ensured and the effect of pharmacologic treatment on suicidal behavior can be assessed.

9.2.4 Role of Life Events in Precipitating Suicidal Behavior

The effects of a recurrent MDE and pessimism are potent predictors of suicide attempts. Given that effective treatments for depression exist and that tertiary strategies for the prevention of depression are available, the fact that this malleable factor is so critical is cause for hope. In particular, since the prevention of life events is likely to be difficult if not impossible, minimization of the recurrence of depression as a possible prevention strategy for suicidal behavior should be imminently attainable. Of course, it has been documented that although training clinicians to treat depression adequately as a suicide prevention strategy is possible, the effects of

training wear off in a relatively brief period of time suggesting that ongoing education for clinicians is key (Rutz 2001).

The role of stressful life events in precipitating suicidal acts requires further elucidation. While secondary analyses suggested that health related and a handful of other life events may play a role, the effects appear not to be as robust as might be anticipated. Nonetheless, potentially malleable factors that moderate the risk for suicidal behavior, such as pessimistic self-appraisal, may be useful targets for interventions for suicide risk reduction.

9.3 Limitations

A limitation of this study is the inclusion of both suicide attempts and suicide completion as one outcome measure. Traits which predict suicide attempt may differ from those that predict suicide completion. Because the base rate of suicide is low even in high risk patient populations, such large samples of clinically well characterized subjects are required to distinguish differences in predictive power for attempt compared to completion that cost and feasibility become critical impediments. This study focused on a high risk population, patients admitted during an MDE. Because an MDE acts as a stressor within the stress-diathesis model we were largely unable to test for the presence of the diathesis for suicidal behavior outside the immediate context of this stressor.

Suicide attempts in this study were relatively few, with 74 attempts over a 2- year period.

Our study followed subjects for only two years. A longer term follow-up may be of interest given that Fawcett et al. (1990) found that short-term predictors of suicide completion differed from long-term predictors. We found that most suicide attempts occur in the first three months after the index evaluation and the rate becomes lower but remains elevated for two years and then drops again. Fawcett et al. (1990) may have been detecting the effects of future new episodes of major depression during the follow-up period from 2 to 8 years after initial evaluation. This later time period remains an area requiring further inquiry.

Many of the stressful life changes items were relatively rare events: there were 14 reports of having a child leave home for college and 58 reports of promotions. Nonetheless, the lack of associations of particular stressful life change items to suicidal acts is remarkable. A considerable strength is that the data on life events was collected completely independently of data regarding suicide attempts, i.e. life events assessments were not triggered by suicide events, protecting against memory bias and mis-ascribing relationships between the act and concurrent life events.

9.3.1 Methods

9.3.1.1 Data not Obtained

There are several types of data that were not obtained in this study. For one, there is no data about psychotherapeutic treatments for MDE. There also are no fine grained measures of substance use during the follow up data. As well, we did not collect information about responses to life events, only about their occurrence. Finally, we also lack detailed information regarding psychotic symptoms during follow up.

9.3.1.2 Bias

The inclusion of individuals treated at a university clinic and exclusion of current substance and alcohol users hamper the generalizability of our findings. For example, the exclusion of current substance abusers may explain our finding that aggression and hostility do not predict suicidal behavior in men. We followed the patients for 2 years only, although this is the period of highest risk for suicidal acts.

9.3.1.3 Analysis

Another limitation is that the statistical analyses to assess sex differences in the hazard ratios by using interaction terms (variable by sex) showed that the interaction terms lacked statistical significance, except in the case of parental separation. These results are reflected in the overlap in confidence intervals for the hazard ratio for women compared to men. It is possible that the smaller number of subjects and fewer future suicidal acts among men led to large differences in the hazard ratio estimates with wide confidence intervals for the two sexes, thus leading to nonsignificant differences. However, we think it is useful to document the hazard ratios within each sex because the order of importance of the individual risk factors differs in men and women. Moreover, in the multivariate models, while previous suicide attempts is an independent predictor for women, among men it is not driving the risk, just “standing in” for other factors.

9.4 New Hypotheses

This work leads to several new hypotheses to be tested in future studies. One is that robust treatment of MDE will decrease the frequency of suicidal acts in a 2 year period. Given the role of serotonin in suicidal behavior, a comparison of serotonergic versus non-serotonergic agents could be instructive, especially since the use of placebo in highrisk groups is problematic. Also, comorbid substance abuse and relapse in use is an unmeasured risk factor in this work despite being common in mood disordered populations and associated with cigarette smoking found to be predictive here. It would be instructive to test whether depressed past substance abusers with

relapse in substance use are at greater risk for suicidal behavior when using substances, while controlling for future MDE and stressors, both linked to relapse for substance use. Finally, it may be of utility to examine biological predictors in these populations. It stands to reason that those individuals who have lower serotonergic function as measured by in vivo assays of brain serotonin transporter and 5HT1a receptors are at greater risk for suicidal behavior prospectively.

9.5 Future Research

In addition to testing the new hypotheses noted above, several other lines of study are worthy. A longer term follow-up would be of interest given that there is evidence that short-term predictors of suicide completion differ from long-term predictors.

It would also be of interest to conduct future studies in larger samples, given the extremely low incidence of suicide attempts and completions.

Also, future large studies in the general population instead of clinical samples would allow for further generalizability of the results.

Future studies of life events and suicidal behavior should include instruments assessing the subject's subjective experience of the life event, and how the individual appraised and coped or responded to the life event, since the same life event may cause different emotional reactions depending on past experience, personality traits, and perceived self-efficacy (Lazarus 1984) (Lazarus 1993; Bandura 1997). Daily hassles or chronic stress, which can also predict suicidal behaviors (Yen, Pagano et al. 2005), should be assessed.

Future studies should include multiple informants whenever possible, to provide independent corroboration of the actual occurrence of the life events and/or suicide attempts.

It would be of interest to prospectively compare the relative influence of life events, mental illness and other risk factors on first-time attempters and repeaters. There is some evidence suggesting that the relation between life events and suicidal behaviors may be stronger for first-time ideators and attempters and that mental illness and hopelessness may be more relevant among repeaters (Neeleman, de Graaf et al. 2004; ten Have, de Graaf et al. 2009). Ideally, a large cohort study with a long-term follow-up period would provide the opportunity to examine predictors and protective factors for suicidal behaviors across the life cycle.

10 CONCLUSIONES

1. Observamos que los tres predictores más sólidos de intentos de suicidio futuros eran los antecedentes de intento de suicidio, la gravedad subjetiva de la depresión, y el consumo de tabaco; cada uno de estos factores tenía un efecto aditivo sobre el riesgo futuro de intento de suicidio. Los análisis factoriales revelaron que la tendencia al pesimismo y la presencia de rasgos agresivos/impulsivos aumentaban el riesgo de intento durante el periodo de seguimiento.
2. Estos hallazgos sugieren que, además de obtener una historia de conductas suicidas previas, la evaluación de la gravedad subjetiva de la depresión, la desesperanza y las razones subjetivas para vivir, la comorbilidad con trastornos de abuso de sustancias incluyendo la nicotina, y los factores de la personalidad como rasgos de personalidad del Cluster B, impulsividad y agresividad, asistirá al clínico en la identificación de pacientes de alto riesgo de conductas suicidas, con el fin de poder monitorizarlos más de cerca.
3. La importancia relativa de los factores de riesgo para las conductas suicidas es diferente en hombres y mujeres con depresión. Desde el punto de vista clínico, en los hombres, comparados con las mujeres, es notable la relativa falta de protección conferida por las razones subjetivas para vivir. Aún es más, pese al hecho bien documentado de que los hombres tienen un riesgo mayor de realizar un suicidio consumado, las mujeres deprimidas con antecedentes de intentos de suicidio presentan mayor riesgo de repetir el intento. Por lo tanto, la evaluación clínica podría ser mejorada considerando la diferencia entre los sexos en la importancia de los factores de riesgo y protectores frente a la conducta suicida.
4. Un episodio de depresión mayor durante el periodo de seguimiento emerge como el más robusto factor predictivo de los intentos de suicidio en nuestro estudio, y subraya la necesidad de realizar un mejor diagnóstico y tratamiento de la depresión mayor.
5. Las intervenciones terapéuticas, incluyendo la profilaxis farmacológica para prevenir la recaída o recurrencia de la sintomatología depresiva o las intervenciones psicoterapéuticas enfocadas al pesimismo, podrían proteger de futuras conductas suicidas a los individuos de alto riesgo.

6. Sin embargo, actualmente el tratamiento antidepresivo de los individuos con depresión es sorprendentemente inadecuado incluso en pacientes con antecedentes de intentos de suicidio, quienes se sabe que tienen mayor riesgo de futuros actos suicidas. Esta deficiencia imposibilita la estimación de los efectos antisuicidas de los antidepresivos en estudios naturalísticos.
7. Son necesarios estudios controlados de antidepresivos para evaluar sus efectos sobre la conducta suicida.
8. Contradiendo nuestra hipótesis y la experiencia clínica, pero consistentemente con algunos estudios previos, no hallamos evidencia de que los acontecimientos vitales actúen como factores precipitantes de los intentos de suicidio.
9. El papel de los acontecimientos vitales estresantes como factores precipitantes de los intentos de suicidio requiere ser aclarado en futuros estudios.
10. Los próximos pasos en la investigación sobre las conductas suicidas deben incluir estudios prospectivos de seguimiento y ensayos clínicos para que este campo pueda avanzar. Los pacientes necesitan herramientas predictivas y de pronóstico para poder mejorar sus tratamientos y reducir las tasas de suicidio.

11 CONCLUSIONS

1. We found that the three most powerful predictors of future suicidal acts were a history of suicide attempt, severe subjective depression, and cigarette smoking, with each of these risk factors having an additive effect on future risk. Similarly, factor analyses revealed that a tendency towards pessimism and the presence of aggressive impulsive traits increased future risk.
2. These findings suggest that in addition to obtaining a history of suicidal behavior, assessment of subjective depressive severity, hopelessness and fewer perceived reasons for living, comorbidity with substance abuse disorders including nicotine, and personality factors such as Cluster B personality disorders, impulsivity, and aggression, will assist the clinician in the identification of patients at higher risk so that they can be monitored more closely.
3. The importance of risk factors for suicidal acts differs in depressed men and women. From a clinical standpoint, the relative lack of protection afforded by reasons for living in men, compared to women, is notable. Furthermore, despite the well-documented fact that men are at greater risk for completed suicide, depressed female suicide attempters appear at relatively greater risk for repeated suicidal behavior. Thus, clinical evaluation may be enhanced by considering the difference between the sexes in the importance of risk and protective factors for suicidal acts.
4. A major depressive episode during the follow-up period emerges as the most robust predictor of suicide attempts in our study and emphasizes the need for better diagnosis and treatment of major depression.
5. Interventions including pharmacotherapeutic prophylaxis to prevent relapse or recurrence of depressive symptomatology or psychotherapeutic interventions targeting pessimism may protect at risk individuals from future suicidal behavior.
6. However, currently antidepressant treatment of depressed patients is strikingly inadequate even in suicide attempters, known to be at higher risk for suicidal acts. This deficiency undermines the ability to measure the antisuicidal effects of antidepressants in naturalistic studies.
7. Controlled studies of antidepressants are needed to evaluate effects on suicidal acts.

8. Contrary to our hypothesis and clinical lore, but consistently with some prior studies, we did not find evidence that life events served to precipitate suicide attempts.
9. The role of stressful life events in precipitating suicidal acts requires further elucidation.
10. Next steps in research on suicide behavior should include prospective follow-up studies and clinical trials to move forward in the field. Patients need predictive and prognostic tools to improve their treatments and to decrease suicide rates.

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13 TABLAS

Tabla 1. Aspectos a valorar en pacientes con conductas relacionadas con el suicidio.	24
Tabla 2. Características de las Submuestras Empleadas en cada Hipótesis.....	43
Tabla 3. Baseline Comparison of Depressed Past Suicide Attempters and Non-attempters: Demographics, Current Psychopathology and Trait Assessments (Full sample, N=430)	44
Tabla 4. Baseline Demographic Features of Suicide Attempters versus Non-attempters with Major Depression (N=308).....	45
Tabla 5. A Baseline Comparison of Depressed Past Suicide Attempters and Non-attempters: Current Psychopathology (N=308). * Wilcoxon's Test Z-score.....	45
Tabla 6. A Baseline Comparison of Depressed Past Suicide Attempters and Non-attempters: Traits Measures (N=308).....	45
Tabla 7. Baseline Demographic Characteristics of Men and Women in a Study of Suicidal Acts in the 2 Years Following a Major Depressive Episode.....	47
Tabla 8. Baseline Clinical Characteristics of Men and Women in a Study of Suicidal Acts in the 2 Years Following a Major Depressive Episode.....	47
Tabla 9. Univariate Cox Proportional Hazards Regression Models Predicting Suicidal Acts by Men and Women in the 2 Years Following a Major Depressive Episode	48
Tabla 10. Multivariate Cox Proportional Hazards Regression Model Predicting Suicidal Acts by Men and Women in the 2 Years Following a Major Depressive Episode	49
Tabla 11. Relation of Baseline Characteristics to Time Between Hospital Discharge and First Suicide Attempt for 134 Patients With Major Depression. Relation to Suicide Attempts During Follow-Up, From Cox Proportional Hazards Analysis (* Mean-centered variable).	50
Tabla 12. Relation of Age, Previous Suicide Attempts, and Follow-Up Characteristics to Time Between Hospital Discharge and First Suicide Attempt in 136 Subjects With Major Depression. Relation to Suicide Attempts During Follow-Up, From Cox Proportional Hazards Analysis (* Mean-centered variable).	50
Tabla 13. Adequacy of Antidepressant Treatment During Follow-Up for Patients Hospitalized for Major Depression With and Without Previous Suicide Attempts. Score for Adequacy of Treatment (range=0-5; adequate= ≥ 3).....	50
Tabla 14. Summary of Recent Life Changes Scale (N=430 subjects, n=228,024 person-days).	51
Tabla 15. Predicting Suicide Attempt Based on Stress.....	51

Tabla 16. Predicting Suicide Attempt Based on Stress.....52

14 FIGURAS

Figura 1. Modelo Estrés-Diátesis.....	20
Figura 2. Taxonomía de los estudios (Lehmann y cols. 1995).....	36
Figura 3. Cumulative Proportion of Patients Who Did Not Attempt Suicide Over a Two-Year Follow-Up Period After a Major Depressive Episode, by Baseline Presence of One, Two and Three of the Most Powerful Predictors of Suicidal Acts.....	46
Figura 4. Relationship Between the Three Strongest Predictors and Other Variables Related to a History of Suicidal Acts.....	46
Figura 5. Additive effect of high scores on the aggression/impulsivity factor and the pessimism factor on future suicidal acts.....	46
Figura 6. Additive effects of obtaining high scores on each of the scales entered into the principal component analyses for the aggression/impulsivity factor (BGA, BDHI, BIS) and the pessimism factor (BDI, BHI, SSI, RFLS).....	47
Figura 7. Nonparametric Survival Curve Estimates of Suicidal Acts by Men and Women in the 2 Years Following a Major Depressive Episode ^a	48
Figura 8. Estimated Survival Curve Indicating Number of Days Between Hospital Discharge and First Suicide Attempt for 136 Patients With Major Depression.....	50

15 APÉNDICES