表2　非定型抗精神病薬の糖尿病のリスク

研究	研究法	調査対象	糖尿病の評価	結果［FPG＝平均値（標準偏差）］	研究の質
Yasui-Furukori et al. (2009)[30]	横断研究	統合失調症の入院患者100名	投与後，最低3ヵ月後のFPG	olanzapine, n＝50, FPG＝92.1(8.9) risperidone, n＝50, FPG＝94.4(10.3)	b), c), h)−1, h−4
長嶺(2006)[12]	横断研究	統合失調症で，非定型薬を単剤投与されている非肥満，非糖尿病患者32名	投与後，最低2週間後のFPG	olanzapine, n＝8, FPG＝93.4(11.4) quetiapine, n＝8, FPG＝92.3(9.7) risperidone, n＝8, FPG＝87.1(9.7) perospirone, n＝8, FPG＝88.3(8.9)	b), c), f)
山田ら(2006)[23]	非無作為化試験	統合失調症の入院患者で，定型薬から非定型薬への切替えが可能な40名（olanzapine，quetiapine と risperidone 投与群は無作為に割り付けたが，糖尿病既往歴・家族歴がある場合は risperidone を割り付け）	切替え24週後のFPG	olanzapine, n＝12, FPG＝90.3(5.7) quetiapine, n＝12, FPG＝95.5(19.1) risperidone, n＝16, FPG＝92.5(9.0)	a), b), d)
村下ら(2004)[11]	症例対照研究	精神科病院に受診する非定型薬を投与された症例659名の中で，治療中に高血糖が認められた症例	糖尿病（以下の基準を2回満たすもの：FPG＞126mg/dL or OGTT＞200mg/dL），高血糖（以下の基準を1回満たすもの：FPG＞126mg/dL or OGTT＞200mg/dL）	olanzapine, n＝54, 2 quetiapine, n＝104, 0 risperidone, n＝147, 1 perospirone, n＝80, 0	b), f)
Togo et al.(2004)[26]	横断研究	統合失調症の患者33名	投与後，最低4週間後のFPG	olanzapine, n＝18, FPG＝89.7(13.5) risperidone, n＝15, FPG＝94.3(11.9)	c)
白土(2004)[22]	コホート研究	統合失調症の入院患者で定型薬を投与されており，非定型薬単剤投与に切り替えた15名	非定型薬処方時の血糖値	olanzapine, n＝7, FPG＝85.0(12.0) risperidone, n＝8, FPG＝86.1(14.3)	b), c)

注）FPG＝Fasting Plasma Glucose；OGTT＝Oral Glucose Tolerance Test
a）研究法は前向きである。
b）統合失調症の診断基準として，ICDまたはDSMを利用している。
c）調査対象は，調査参加の登録時（ベースライン時）に糖尿病ではない患者に限定している。
d）調査参加の登録は，連続抽出法か無作為抽出法を用いている。
e）抗精神病薬の暴露は，客観的方法を用いて確認している。
f）糖尿病に関する評価は，日本糖尿病学会の基準[17]を用いてなされている。
g）抗精神病薬と糖尿病の関係を調べるために，少なくとも1年以上の追跡をしている。
h）糖尿病の主要な以下の6つのリスク要因を統制している：(1) Body Mass Index（BMI），(2) 第1親等の糖尿病既往歴，(3) 人種，(4) 年齢，(5) 身体活動量，(6) 社会経済的状況。

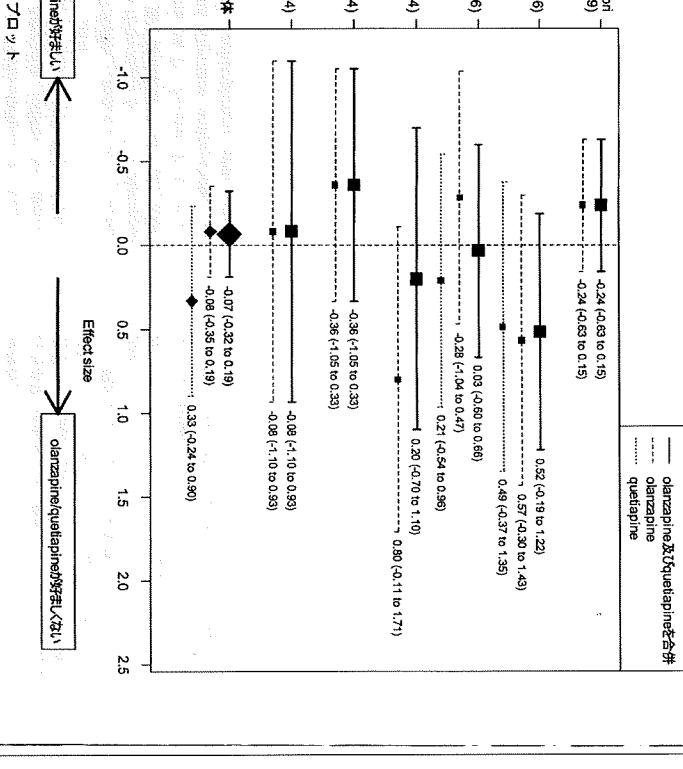

図2　フォレスト・プロット
四角（■）およびダイヤ（◆）はHedgesのg値であり，その両脇の線は95%信頼区間を示す。実線はolanzapineおよびquetiapineを合併した値，ダッシュはolanzapineの値，ドットはquetiapineの値を示す。Hedgesのg値は，正の値が高いほどolanzapineまたはquetiapineが他の抗精神病薬よりも好ましくないこと，負であるとその逆を意味する。

と，olanzapineとquetiapineは，他の抗精神病薬と比べ，糖尿病のリスクについて差がみられなかった（g＝−0.07，95%CI＝−0.32 to 0.19）。また，olanzapineとquetiapineを別にしてメタ分析を行っても同様の結果が得られた。そして，適格基準に該当した各々の研究は，方法論上の限界があることが明らかになった。

表1に示したように我が国で認可されている非定型抗精神病薬7剤のうち，添付文書において，olanzapineとquetiapineは，糖尿病の患者あるいは既往歴のある患者への使用が禁忌となっている。糖尿病の病態には民族差があることが指摘されているため[10]，抗精神病薬の添付文書の糖尿病に関する注意喚起（警告および禁忌等）の設定についての妥当性を検討するためには，対象となった人種や投薬期間など，臨床試験や調査の研究法を十分に吟味する必要がある。

本研究では，日本人の統合失調症患者において，olanzapineとquetiapineは，他の抗精神病薬と比べ，糖尿病のリスクについて差がみられなかったものの，この結果の解釈には注意を要する。その理由として，Smithら[27]のメタ分析の結果と同様に，本研究においても，前向きにデータを収集している研究は少なく（16.7%），1次研究のエビデンス・レベル[9]に問題が残されているからである。また，メタ分析では，各々の研究の

特性が不均質である場合に，すべての研究を統合することは，リンゴとオレンジを混ぜるようなものであると批判されることがある（apples and oranges problem）[2]。本研究では，母数モデルの妥当性は等質性の検定により支持されていたため，この問題は生じていないことが期待できるものの，適格基準に該当した研究が6研究に過ぎないために検出できなかった，研究結果の異質性に寄与する要因がある可能性は考えられる。今後の研究では，clozapine（平成21年4月に我が国で承認）を含めた非定型抗精神病薬の使用経験を蓄積し，各薬剤間の糖尿病のリスクを十分に比較検討した上で，注意喚起の設定の妥当性について再評価していく必要があると考える。

また，適格基準に該当した6編の研究は，非暴露群として，risperidone（100%）とperospirone（33.3%）を取りあげていたが，他の非定型および定型抗精神病薬については取りあげていなかった。Smithら[23]のメタ分析においても，比較的新しい非定型抗精神病薬であるziprasidone，amisulpride，aripiprazoleの糖尿病のリスクを検討している研究はなかった。今後の研究では，国際的にも，比較的新しい非定型抗精神病薬の糖尿病のリスクを評価することが必要と考えられる。さらに，国際的には定型抗精神病薬と非定型抗精神病薬の糖尿病のリスクを比較している研究が数多くあるものの[29]，我が国では検討されていないため，定型抗精神病薬の糖尿病のリスクも併せて評価していく必要性がある。

脚　注

注1　研究の初期段階では，risperidoneの販売開始年を基準として1996年から2009年2月26日までの文献を検索し，適格基準として2種類以上の抗精神病薬の糖尿病のリスクを検討している研究としたが，該当する文献がなかった。

注2　適格基準から除外された文献リストの要望があれば，第1著者まで連絡されたい。

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abstract

Pharmacotherapy of atypical antipsychotics and risk for diabetes in schizophrenia : a meta-analysis

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Background : Among seven atypical antipsychotics approved for the treatment of patients with schizophrenia, olanzapine and quetiapine are contraindicated in patients with diabetes in Japan.

Objective : To compare diabetes risk of olanzapine and quetiapine with that of other antipsychotics in patients with schizophrenia in Japan.

Method : We performed a literature search using MEDLINE and Japana Centra Revuo Medicina between January 2001 and February 2009. We assessed studies that met the following criteria : (1) comparison of diabetes risk between olanzapine or quetiapine and other antipsychotics, (2) patients with schizophrenia in study population, and (3) journal article other than case- or case-series study. A fixed effects model was used for the meta-analysis.

Results : Six studies including one prospective study met the inclusion criteria. Compared with olanzapine and quetiapine, the diabetes risk of other antipsychotics was not significantly different (k＝6, g＝－0.07, 95% CI＝－0.32 to 0.19).

Conclusion : This meta-analysis suggests careful re-evaluation of the warning statement in the package insert on diabetes risk among patients treated with antipsychotics.

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植込み型除細動器(ICD)患者の抑うつおよび不安に対する精神科的支援の現状と展望

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抄録：植込み型除細動器(ICD)は，致死性不整脈による心臓突然死を予防する機器として発展している。しかし，ICD患者は，ショック作動などの特異的な経験により心理社会的問題を抱えているとされている。そこで本研究においては，ICDにおけるショック作動が抑うつや不安などの精神症状に及ぼす影響についての観察研究，およびICD患者に対する心理社会的介入研究について検討し，ICD患者の精神科的支援の現状と展望について論じることを目的とする。方法としては，観察研究および介入研究を収集したうえで，適格基準に当てはまる論文を選定した。その後，それらの研究の特徴を抽出し，介入研究に関してはメタ分析を行い，効能の検討を行った。その結果，まず観察研究においては，ショック作動と抑うつや不安などの精神症状との関連について一致した結論は得られなかった。また，介入研究においてもメタ分析の結果，効能は認められなかった。今後の研究への展望として，まず観察研究では，ショック作動と精神症状の関連に関与する交絡変数を考慮したうえで，知見を重ねる必要がある。また，介入研究では，研究の質を高めて効能を検討し直す必要があり，今後は精神症状を呈した患者に対するターゲット・アプローチの開発も期待される。

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Key words：植込み型除細動器(implantable cardioverter defibrillator)，心理社会的介入(psycho-social intervention)，抑うつ(depression)，不安(anxiety)，作動(shock)

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1 はじめに

心臓突然死の原因となる心室細動や心室頻拍などの致死性不整脈の治療法として，植込み型除細動器(Implantable Cardioverter Defibrillators；以下ICDと略記)が1980年に米国で初めて使用された。ICDはペースメーカーに電気ショックの機能を加えた機器であり，重篤な不整脈が発生した際に電気ショックが流れることにより突然死を防ぐものである。メタ分析の結果から，ICD植込みは，抗不整脈薬の使用と比較して，不整脈による突然

Psychiatric supports for depression and anxiety of patients with an implantable cardioverter defibrillators; A review and future recommendations

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死を50％低減させることが明らかとなっている（HR 0.50，95％ CI 0.37～0.67）[9]。また本邦においても，ICD植込みに関する研究が積極的に進められ，1996年には保険償還がなされた。近年では，手術の簡便化や機器の軽量化がなされたこともあり，ICDの症例数も，90年代までは500件以内にとどまっていたのに対し，2005年には3,000件にまで増加している[29]。さらにICDは，心不全や拡張型心筋症，また心筋梗塞後の患者に対して致死性不整脈の一次予防としての適用の有効性も示されている[30]。

以上のように，ICD植込みは患者にとって生命予後の改善という恩恵があるが，その一方でICDのショック作動は胸痛や衝撃，恐れなどを招くため[16]，ICD患者の心理社会的問題に焦点が当てられるようになってきている[5,35,40]。そこで本稿では，ICDのショック作動と抑うつや不安との関連を検討した観察研究，およびICD患者の呈する抑うつと不安に対する介入研究を展望し，今後のICD患者に対する有益な精神科的支援のあり方について考察することを目的とする。

2 観察研究

ICD患者のうち24～46％が抑うつ症状，24～87％は不安症状を呈していることが，系統的展望により示されている[37]。このような精神症状を呈する一因として，特にICDショックの作動経験があると考えられている。ICD患者に対してその特徴を横断的に検討した研究では，約半数が致死性の不整脈が発生した際のショック作動を経験しており，このようなショック作動は，胸痛や強い衝撃を伴い，患者に恐怖心を与えるものであると報告されている[16,20]。また，24時間以内に3回以上の作動を起こす頻回作動（storm）を経験した患者は，植込み後の2年間に10％存在していることが示されており，これらの頻回作動が抑うつや不安に影響を及ぼすとの知見も得られている[11,28]。そこで本節では，ICD患者におけるショック作動と抑うつや不安との関連についての研究を展望し，今後の研究の課題を考察する。

1．方法

1）文献収集

1980年1月～2009年4月までに行われた，ICD患者におけるショック作動と抑うつおよび不安の関連について検討している研究を，文献データベースとしてMEDLINEとPsycINFOを用いて検索した。

2）適格基準

適格基準として，以下の5つの基準を採用した：（1）調査対象は，ICD患者である，（2）ショック作動経験の有無による群分けを行って分析をしている，（3）目的変数として抑うつまたは不安を測定している，（4）出版されている論文である，（5）英語の論文である。

3）情報の抽出

著者の2人（K.I.，Y.O.）が，適格基準に合致している文献を収集し，おのおのの文献から，下記の情報を抽出した：（1）研究法，（2）適格基準，（3）標本サイズ，（4）評価項目，（5）群ごとの抑うつまたは不安に関する指標の差異。

2．ICD患者の抑うつ症状

上記の手続きの結果，ICD患者におけるショック作動と抑うつの関連について検討した研究は5編であり（表1），そのうち2編において，群間で得点差がみられた。Jacq ら（2009）[21]は，作動を経験していない患者と比較して，作動を経験している患者で有意に抑うつ得点が高いことを示している。また，Prudente ら（2006）[34]は，実際には作動が起きていないが，作動が起きていると患者が思い込んでいる「疑似作動」に注目し，疑似作動を経験している患者は，本当の作動を経験している患者および作動を経験していない患者と比較して，有意に抑うつ得点が高いことを示している。

3．ICD患者の不安症状

上記の手続きの結果，ICDのショック作動と不安に関する検討を行った観察研究は6編であり（表1），そのうち4編において，群間で得点差がみられていた。Prudente ら（2006）[34]は，不安と同様に，疑似作動を経験している患者は，本当の作動を経験している患者および作動を経験していない患者と比較して，有意に不安得点が高いことを示している。一方，Bilge ら（2006）[2]とJacq ら（2009）[21]は，作動を経験していない患者と比較して，作動を経験している患者で有意に不安得点が高いことを示している。また，Van den Broek ら（2008）[41]は，縦断的な調査を行い，植込み後2カ月後に作動を経験している患者は，作動を経験していない患者と比較して，植込み時から2カ月後までの不安得点が有意に上昇していることを示している。

4．ICD患者の抑うつおよび不安に関する今後の研究への展望

観察研究においては，ICDのショック作動と抑うつや不安との関連について一致した結論は得られていない。有意差がみられなかった研究では，限界点として，作動経験の有無を自己報告により測定しているためバイアスが生じる可能性が指摘されている[32]。さらに，今回検討した先行研究では，作動経験からの期間を測定しているものは，1編のみであった[2]。そのため，作動経験からの期間の影響について交絡している可能性も考えられる。

Sears ら（1999）[37]の系統的展望によると，ICD患者においては，死への恐れ，作動への恐れ，デバイスに対する依存心が抑うつや不安の症状を上昇させることが示されている。また，作動と破局的認知（たとえば，「次に作動が起きたら死んでしまうのではないか」といった認知[31]）や抑うつ的な対処行動[17]との関連も示されている。これらのことから，今後研究を進めていくうえで，さまざまな交絡変数の存在を考慮に入れ，作動と抑うつや不安との関連を検討する必要があるといえる。

先行研究では，ショック作動が抑うつと関連することを検討する研究ばかりでなく，逆の因果として，重篤な抑うつ症状がショック作動を引き起こすとの知見が得られている。Whang ら（2005）[44]は，ICD患者を対象に，ショック作動の予測因子を検討した結果，重篤な抑うつ症状が心室細動や心室頻拍の予測因子となることを示している。また，その他のネガティブな感情に関しても，不整脈発作を引き起こすことが示されている[13,20]。したがって，ICD患者の抑うつ症状を予防・管理していくことは疾病管理においても重要な課題であるといえる。今後は先に述べた問題点を考慮したうえで，観察研究による知見がさらに積み重ねられることで，精神症状による作動の誘発を軽減し，作動の悪循環を断ち切ることが期待できる。

3 介入研究

近年，ICD患者が呈する精神症状に対する無作為化比較試験も蓄積されつつある。本節では，メタ分析により精神症状に対する介入法の効能の程度を検討することを目的とする。

1．方法

1）文献収集

Pedersen ら（2007）[33]は，文献データベースとしてMEDLINEとPsycINFOを用いて，1980年1月～2007年4月までに行われた，ICD患者への心理社会的介入法の効能を検討している研究を系統的に収集している。本研究では，Pedersen ら（2007）[33]が収集した9編のうち，評価項目として抑うつまたは不安を測定し，研究法が無作為化比較試験である5編を分析対象とした。さらに，2009年6月時点までに出版された，ICD患者への抑うつまたは不安への介入法の効能を，無作為化比較試験により検討している研究を，文献データベースとしてMEDLINEとSocial Science Citation Indexを用いて検索した。

2）適格基準

適格基準として，以下の5つの基準を採用した：（1）調査対象は，ICD患者である，（2）研究法は無作為化比較試験（クラスター無作為化試験を含む）である，（3）評価項目として抑うつまたは不安を測定している，（4）出版されている論文である，（5）英語の論文である。

3）情報の抽出

著者の2人（K.I.，Y.O.）が，適格基準に合致している文献を収集し，おのおのの文献から，下記の情報を抽出した：（1）国，（2）調査対象，（3）標本サイズ，（4）最終追跡症例数，（5）適格基準，（6）介入内容，（7）介入の実施者，（8）介入期間，（9）介入時期，（10）介入頻度，（11）対照群の設定，（12）研究終了時の群ごとの抑うつまたは不安に関する指標の値，（13）評価時点，（14）研究の質にかかわ

表1 ICD患者の作動と抑うつおよび不安の関連

研究	研究法	適格基準
Pauli et al (2001) [32]	横断研究	収集基準：ICD患者のうち，60歳未満の者 除外基準：(1) 精神的問題で回答が難しい者，(2) ドイツ語が話せない者，(3) 話番号が入手不可な者
Kamphuis et al (2003) [22]	横断研究	収集基準：ICD患者132名，非ICD患者35名（1998～1999年の間に大学病院3施設もしくは一般病院1施設のいずれかに来院した患者） 除外基準：NA
Prudente et al (2006) [34]	横断研究	収集基準：ICD患者のうち，18歳以上の者（2001～2003年の間に来院した患者） 除外基準：NA
Bilge et al (2006) [2]	横断研究	収集基準：ICD患者のうち，心室性不整脈により適用となった者（1995～2005年の間に来院した患者） 除外基準：(1) 状態の悪い精神疾患を併発している者，(2) 植込み3カ月以内の者
Van den Broek et al (2008) [41]	縦断研究	収集基準：ICD患者のうち，18～80歳の者（2003～2007年の間に来院した患者） 除外基準：オランダ語の読みと理解のできない者
Jacq et al (2009) [21]	横断研究	収集基準：ICD患者のうち，16歳以上の者で同意を得た者 除外基準：医学的あるいは，手術の問題で，インタビュー調査への参加が困難な者

注）STAI=State-Trait Anxiety Inventory[39]；BAI=Beck Anxiety Inventory[1]；BDI=Beck Depression Inventory[19]；CES-D=Centre for Epidemiologic Studies Depression scale[43]；HAD=Hospital Anxiety and Depression Scale[38]；STAI#=ドイツ語版STAI[24]；STAI##=オランダ語版STAI[42]；STAI-S=STAI-State anxiety; STAI-T=STAI-Trate anxiety; NA=Not Available（論文中未記入）；NS=Not Significiant
a=p<.01
b=p<.05
c=p<.10

る情報。

4)研究の質の評価

非薬物療法の無作為化比較試験のための報告の質の基準[3,4]を参考にして作成した，以下の基準を用いて，適格基準に該当した研究の質を評価した。

a)乱数生成の方法として乱数生成器または乱数表を使用しているか，また，無作為化に制限(置換ブロック法，層別無作為化法，最小化法など)を加えている場合は具体的に記述しているか。

b)検定力分析の記述をしているか。

c)介入法の標準化の詳細を記載しているか。例えば，介入者が均質な治療を行うようにするための訓練に用いた，マニュアル，ガイドラインや教材などを引用しているか。

5)統計解析

各研究について，研究の終了時点(終了時点の値が欠損の場合は，値が記載されている中で最も終了時点に近いもの)の抑うつまたは不安に関する平均値，標準偏差および標本サイズから，Hedgesのg値およびその標準誤差を算出した。母数モデルのメタ分析により，おのおのの研究の効果量および標準誤差から，統合された効果量およびその95%信頼区間を求めた[10]。なお，母数モデルの妥当性を評価するため，有意水準を5%として，等質性の検定を行った。等質性が満たされない場合は，変量モデルのメタ分析を行った[10]。

表1 ICD患者の作動と抑うつおよび不安の関連

(1) 作動群 (n=12) (2) 未作動群 (n=12)	STAI# BAI BDI	NS NS NS
(1) A∩B群 (n=6) (2) A群 (n=9) (3) B群 (n=20) (4) C群 (n=97) (A：前の作動から6カ月以内に作動があった人，B：前の作動から6～12カ月の間に作動があった人，C：ここ1年は作動がない人)	STAI#-T STAI#-S CES-D	NS NS NS
(1) 疑似作動群 (n=19) (2) 作動群 (n=28) (3) 未作動群 (n=28)	CES-D STAI-T STAI-S	a (1>3) b (1>3, 1>2) b (1>3, 1>2)
(1) 作動群 (n=56) (2) 未作動群 (n=35)	HAD (depression) HAD (anxiety)	NS b (1>2)
(1) 作動群 (n=16) (2) 未作動群 (n=160)	STAI##	a (1>2) *植込み2カ月後
(1) 作動群 (n=40) (2) 未作動群 (n=25)	HAD (depression) HAD (anxiety)	b (1>2) c (1>2)

2. 無作為化比較試験の特徴

上記の手続きの結果，ICD患者が呈する抑うつおよび不安への介入法の効能を検討した無作為化比較試験は8編であった(表2)。無作為化比較試験で効能が検討されている介入法は，薬物療法ではなく，認知行動療法などの心理社会的介入法に限定される。また，これらの心理社会的介入法は，ICD患者の一部である気分障害や不安障害を呈する患者を対象とするのではなく，ICD患者の全症例を対象としている。すなわち，現在のところ効能が検討されている介入法は，ポピュレーション・アプローチによる心理社会的介入法である。

また，これらの心理社会的介入法の実施者および介入期間は多様であった。介入の実施者が，心理士(大学院生を含む)である研究が5編(62.3%)，看護師である研究が3編(37.5%)，精神科医または研究者である研究が1編(12.5%)であった。介入期間は，1～3カ月のものが6編(75.0%)，1日または9カ月のものが1編(12.5%)であった。さらに介入内容に用いられた技法については，ICD機器や疾患に関する心理教育が6編(75.0%)，認知再構成法が1編(12.5%)，ストレスマネジメントが4編(50.0%)，リラクセーションなどのセルフヘルプが4編(50.0%)であった。

3. メタ分析

まず，メタ分析に必要な統計量が報告されている5編(62.5%)の研究の統計量を基に，ICD患者が呈する抑うつおよび不安への心理社会的介入法の効能を検討した。各研究の効果量は図1のとおりである。次に，研究間の等質性の検定を行ったところ，不安において，研究間の異質性がみられたため(Q17.97，df 4, p<.05)，変量モデルのメタ分析を行った。分析の結果，抑うつ(g0.17，95% CI-0.09 to 0.43)，および不安(g0.38，95% CI -0.10 to 0.86)ともに効果量に差は認められなかった。

表2 ICD患者への心理的社会的介入の抑うつ及び不安への効能①

文献	研究対象
Kohn et al (2000) [23]	国：アメリカ合衆国 対象：2つの大都市の病院において，1998年10月から1998年5月にICDが適用となった61症例を連続登録 標本サイズ：25（介入群）vs 24（対照群） 最終追跡症例数：18（介入群）vs 18（対照群） 適格基準：(1) 研究参加に同意，(2) 認知機能の障害が重篤でない，(3) 基準時まで生存している
Fitchet et al (2003) [15]	国：イギリス 対象：ICDを植込み，心臓リハビリテーションが必要な73症例を連続登録 標本サイズ：8（介入群）vs 8（対照群） 最終追跡症例数：7（介入群）vs 4（対照群） 適格基準：(1) 運動が可能，(2) NYHA心機能分類がIV度ではない，(3) 狭心症ではない，(4) 同意能力がある
Dougherty et al (2004) [12]	国：アメリカ合衆国 対象：突然心停止または致死性の心室性不整脈の蘇生患者のうち，初めてICDを植込み，2000年2月から2001年12月の間に入院していた243症例 標本サイズ：84（介入群）vs 84（対照群） 最終追跡症例数‡：79（介入群）vs 79（対照群） 適格基準：(1) 英語の読み，書き，会話ができる，(2) 電話での連絡が可能，(3) 1年後の追跡調査への協力意志がある，(4) 外来診療できる程度の病状，(5) 21歳以上，(6) 認知機能の障害が重篤でない
Frizelle et al (2004) [18]	国：イギリス 対象：ICD植込みにより生存している85症例 標本サイズ：12（介入群）vs 10（対照群） 最終追跡症例数：12（介入群）vs 9（対照群） 適格基準：(1) 慢性心疾患から不整脈が発症したICD患者（ICD植込み前に冠動脈バイパス術などの手術経験のある患者を含む），(2) 冠動脈バイパス術や心移植を待機している症例ではない，(3) 心室性不整脈ではない，(4) 病状が深刻で，共同作業が不可能ではない，(5) 英語の読み書きができる

注）ICD=Implantable Cardioverter Defibrillators; BDI=Beck Depression Inventory[19]；STAI=State-Trait Anxiety Inventory[39]；NA=Not Available（論文中未記入）；HAD=Hospital Anxiety and Depression scale[38]；NYHA=New York Heart Association; CES-D=Center for Epidemiologic Studies Depression scale[43]]；DASS=Depression Anxiety Stress Scales[27]；HAM-A=HAMilton Anxiety scale in French[6]；CCS=Canadian Cardiovascular Society.

† 特性不安（STAI-T）の評価も行っているが，メタ分析では状態不安（STAI-S）の結果を用いた。

‡ 内訳は不明であるが，両群の標本サイズが等しいと仮定した。

§ 標本サイズの内訳は不明であるが，最終追跡症例数の内訳は合併した集団の平均値の公式より，両群が同数であることが確認できる。

¶ 研究法は，クラスター無作為化試験である。

a) 乱数生成および制限を加えている場合の記述をしている。

b) 検定力分析の記述をしている。

c) 介入法の標準化の詳細を記載している。

表2 ICD患者への心理的社会的介入の抑うつ及び不安への効能①

介入	評価尺度	評価点
介入：認知行動療法（不安，回避行動，作動への恐怖，ストレスマネジメント，復職支援，ICDの安全性などの認知のゆがみ） 実施者：心理学の博士課程の大学院生1名 介入期間：約9カ月 介入時期：ICD植込み前，退院前，外来診療時 介入頻度：ICD植込み前と退院前は30～60分，初めの4週間は毎週1回15～30分，追跡期間（1，3，5，9カ月時）は15～30分の介入 対照：未治療（介入群と同様に，外来診療として1，3，5，9カ月時に追跡）	抑うつ（BDI-II）：M6.9，SD5.9（介入群）vs M15.0，SD13.0（対照群） 不安（STAI-S）†：M32.3，SD9.8（介入群）vs M39.9，SD15.4（対照群） 評価時点：退院後9カ月時	
介入：運動療法，心理教育，心理療法（ICDに関する知識，不安・怒り・抑うつのマネジメント，セルフヘルプ） 実施者：循環器疾患の治療経験のある健康心理士1名 介入期間：12週間 介入時期：ICD植込み後 介入頻度：NA 対照：通常診療	抑うつ（HAD）：NA 不安（HAD）：NA 評価時点：介入後12週間後	
介入：小冊子（回復期の経験談，回復期に成功した技術の説明），電話相談（ICDの知識と行動技術，疾患への対処に関するセルフ・エフィカシーの向上，感情の浮き沈みおよび不安の抑制），緊急相談窓口 実施者：循環器科の臨床経験が5年以上であり，電話相談の訓練を受けた看護師 介入期間：2カ月 介入時期：ICD植込みの退院後 介入頻度：小冊子は退院後1週間以内に読む，電話相談は毎週1回15～20分の介入，緊急相談窓口は24時間無料で電話相談可能 対照：通常診療（ICDに関する教育）	抑うつ（CES-D）：M 9.2，SD 9.3（介入群）vs M 8.6，SD 8.8（対照群） 不安（STAI-S）：M 32.0，SD 11.7（介入群）vs M 33.0，SD 11.2（対照群） 評価時点：退院後3カ月時	b，c
介入：認知行動療法（運動療法，心理教育，心理療法，リラクセーション） 実施者：健康心理士1名 介入期間：3カ月 介入時期：NA 介入頻度：リハビリテーション・プログラムは6週間目までは毎週1回120分の介入，9週目に電話相談，12週目に最終ミーティング 対照：治療待機	抑うつ（HAD）：NA 不安（HAD）：NA 評価時点：介入後12週間後	

表2 ICD患者への心理的社会的介入の抑うつ及び不安への効能②

研究	調査対象
Chevalier et al (2006) [6]	国：フランス 対象：臨床試験の前にICDを植込んだ患者および，臨床試験の間にICDを植込んだ253症例を連続登録 標本サイズ：35（介入群）vs 35（対照群） 最終追跡症例数：13（介入群）vs 16（対照群） 適格基準：(1) 致死的な心室頻拍の既往歴がある，(2) 18～75歳，(3) 住居が病院から遠方ではない，(4) 心理療法を受けた経験がない，(5) 睡眠作用のある向精神薬を使用していない
Sears et al (2007) [36]	国：アメリカ合衆国 対象：ICD患者の中で，過去1年間に少なくとも1回は作動を経験した症例 標本サイズ§：15（介入群）vs 15（対照群） 最終追跡症例数§：10（介入群）vs 10（対照群） 適格基準：NA
Edelman et al (2007) [14]	国：オーストラリア 対象：ICD植込み予定の27症例 標本サイズ：13（介入群）vs 9（対照群） 最終追跡症例数：NA（介入群）vs NA（対照群） 適格基準：(1) 精神病症状を示す疾患ではない，(2) 認知機能の障害が重篤でない，(3) 英語能力が十分である
Lewin et al (2009) [25] ¶	国：イギリス 対象：2004年2月から2005年5月の間に初めてICDを植込んだ268症例を連続登録 標本サイズ：71（介入群）vs 121（対照群） 最終追跡症例数：54（介入群）vs 97（対照群） 適格基準：(1) ICDを1カ月に5例以上植込んでいる施設，(2) 介入法の訓練に参加できる施設，(3) 18歳以上の症例，(4) 同意能力があり，研究参加に同意した症例，(5) 循環器医により症状が安定していると判断されている症例，(6) 冠動脈バイパス術や心移植を待機している症例ではない，(7) 運動誘発性不整脈を患っていない，(8) CCSの狭心症重症度分類でクラスⅢまたはⅣではない，(9) 精神病症状を示す疾患の既往歴がない

注 ）ICD=Implantable Cardioverter Defibrillators; BDI=Beck Depression Inventory[19]；STAI=State-Trait Anxiety Inventory[39]；NA=Not Available（論文中未記入）；HAD=Hospital Anxiety and Depression scale[38]；NYHA=New York Heart Association; CES-D=Center for Epidemiologic Studies Depression scale[43]］；DASS=Depression Anxiety Stress Scales[27]；HAM-A=HAMilton Anxiety scale in French[6]；CCS=Canadian Cardiovascular Society.
†特性不安（STAI-T）の評価も行っているが，メタ分析では状態不安（STAI-S）の結果を用いた。
‡内訳は不明であるが，両群の標本サイズが等しいと仮定した。
§標本サイズの内訳は不明であるが，最終追跡症例数の内訳は合併した集団の平均値の公式より，両群が同数であることが確認できる。
¶研究法は，クラスター無作為化試験である。
a）乱数生成および制限を加えている場合の記述をしている。
b）検定力分析の記述をしている。
c）介入法の標準化の詳細を記載している。

表2 ICD患者への心理的社会的介入の抑うつ及び不安への効能②

介入法	評価と結果	研究の質
介入：認知行動療法（ストレスマネジメント，リラクセーション，認知再構成法，コミュニケーション，問題解決療法） 実施者：認知行動療法を実施する資格を持ち，不安障害の治療経験のある，臨床心理士と精神科医各1名 介入期間：3カ月 介入時期：NA 介入頻度：2週間に1回，120分の介入 対照：通常診療	抑うつ（BDI-13）：M 4.9, SD 3.5（介入群）vs M 6.1, SD 4.5（対照群） 不安（HAM-A***）：M 2.6, SD 1.5（介入群）vs M 9.0, SD 4.3（対照群） 評価時点：介入開始後12カ月時	a, b
介入：ストレスマネジメント 実施者：ICD植込み患者へのストレスマネジメントと認知行動療法の経験を持つ研究代表者1名と研究補助者 介入期間：6週間 介入時期：NA 介入頻度：1週間に1回，90分の介入 対照：介入群に行う内容を圧縮した講義を，1日4時間をかけて行う	抑うつ（CES-D）：M 6.3, SD 6.3（介入群）vs M 7.9, SD 4.4（対照群） 不安（STAI-T）：M 32.8, SD 4.9（介入群）vs M 31.3, SD 5.5（対照群） 評価時点：介入終了直後	
介入：心理教育（ICD，作動，生活習慣，コミュニケーション） 実施者：循環器科の看護師と臨床心理士各1名 介入期間：1日 介入時期：ICD植込みの2週間後 介入頻度：60～90分の介入 対照：通常診療（循環器医からの口頭説明と小冊子の配布）	抑うつ（DASS）：NA 不安（DASS）：NA 評価時点：介入後6カ月後	
介入：セルフヘルプ（患者用の小冊子，家族用の小冊子，目標管理用の日記，リラクセーションのテープまたはCD），電話相談（経過の検討，成功体験の強化，新しい目標設定） 実施者：臨床心理士による訓練を受けた看護師 介入期間：12週間 介入時期：ICD植込み前，退院後 介入頻度：ICD植込み前の小冊子は20分の説明，退院後（1, 3, 6週間時）の電話相談は15分の介入 対照：通常診療（ICDに関する小冊子を配布し，手術後の経過を観察する）	抑うつ（HAD）：M 3.9, SD 4.3（介入群）vs M 4.3, SD 4.3（対照群） 不安（HAD）：M 5.3, SD 0.4（介入群）vs M 5.5, SD 3.5（対照群） 評価時点：ICD植込み後6カ月時	a, b, c

4 介入研究の問題点と今後の展望

メタ分析により，ICD患者が呈する抑うつおよび不安への心理社会的介入法の効能が認められないことが示されたものの，この結果の解釈には注意を要する。先行研究の課題として，(1)検定力，(2)介入方法，(3)脱落率の3点がある。

第1に，対応のないt検定（両側検定，有意水準5%）を行う際に検定力が80%以上となるための標本サイズを求めると，母集団効果量が大きい（δ=0.8）と仮定した場合は各群26，中程度（δ=0.5）と仮定した場合は各群64以上の症例が必要となる[7]。つまり，これまでの先行研究は，仮に大きい母集団効果量を期待しても，Doughertyら（2004）[12]とLewinら（2009）[25]を除き，検定力が80%に満たないという問題が残される。したがって，今後の研究では，適切な標本サイズを設計したうえで，効能を検討する必要があると考えられる。

第2に，介入方法については，治療者に対する教育を行っていることを明記している研究は，2

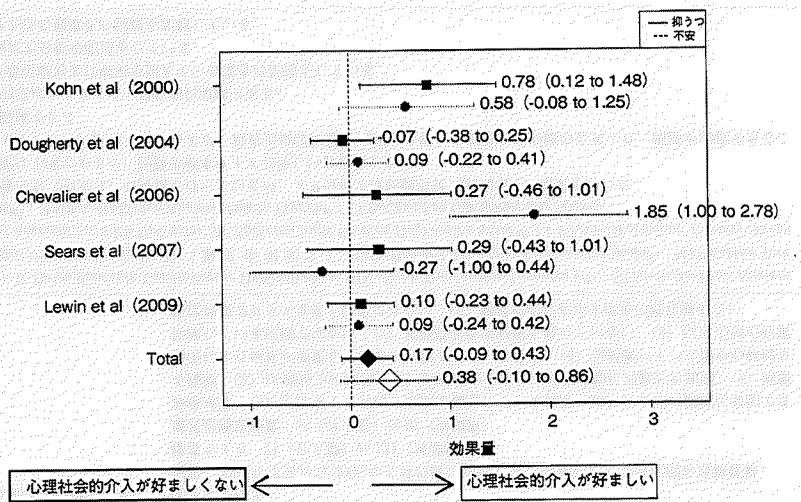

図1 フォレストプロット
四角(■)および丸(●)はHedgesのg値であり，その両脇の線は95%信頼区間を示す。実線は抑うつ，点線は不安の値を示す。Hedgesのg値は，正の値が高いほど対照群よりも心理社会的介入の方が好ましいこと，負であるとその逆を意味する。

編(25.0%)[12,25]にとどまっているという問題がある。そのため，多くの研究は，介入の標準化が十全ではないといえるであろう。

第3に，脱落率について，多くの先行研究の限界として指摘されていた。先行研究における，脱落率は研究間の散らばりが大きく，中央値が26.5%，最小値が4.5%，最大値が58.6%であった。

以上のような問題を考慮したうえで，今後の研究ではより質の高い無作為化比較試験を蓄積する必要がある。その際，自己記入式尺度による評価ばかりでなく，再入院率などを評価指標として含め，費用対効果を求めていく試み[25]も重要になると思われる。さらに，現在のところ効能が検討されている介入法は，ICD患者の全症例を対象とする心理社会的介入法であるが，気分障害や不安障害を呈する患者を対象とするようなターゲット・アプローチによる介入の効能も検討していく必要があると考える。例えば，アメリカ心臓協会は，循環器疾患の通常診療の中で，自己記入式尺度を用いてうつ病をスクリーニングし，重症度が中等症以上の患者は精神科に紹介するように勧告を提出している[26]。このような精神科と循環器科の連携を強化するような試みの効能を検討していくことが求められるであろう。

なお，このメタ分析は，(1)系統的な文献検索をしていないこと，(2)未出版の文献を含めて網羅的な文献検索をしていないこと，(3)複数の評価者により，情報を抽出していないという3点の限界が残される。

5 まとめ

本稿の目的は，ICDのショック作動により引き起こされる抑うつや不安に関する観察研究，およびその予防や管理のための介入研究の知見から，今後のICD患者に対する有益な精神科的支援について考察することであった。その結果，第1に観察研究においては，ICD特有の心理社会的問題であるショック作動との関連についての一貫した知見は得られていなかった。また，ICD患者が呈する抑うつおよび不安への心理社会的介入法の効能は認められず，従来の無作為化比較試験には，検定力，介入方法，脱落率の点に課題が残されることが示された。

したがって，今後の展望として，(1)作動と精神症状の関連における交絡変数を検討すること，(2)より質の高い無作為化比較試験により，ICD患者に対する心理的社会的介入法の効能を検討することが求められる。このような点に関する検討を行うことで，ICD患者の精神症状発症のメカニズムが明らかとなり，ICD患者が呈する精神症状に対する診断・治療のために精神科と循環器科との緊密な連携が促進されることが期待される。

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Summary

Psychiatric supports for depression and anxiety of patients with an implantable cardioverter defibrillators: A review and future recommendations

ICHIKURA Kanako et al

Background: The implantable cardioverter defibrillator (ICD) has proved effective in preventing sudden cardiac death. However, ICD patients potentially face significant psychosocial issues because of their risk for life-threatening arrhythmias and the occurrence of ICD shock.

Objective: This review provides an overview of (1) relationship between ICD shock and psychological status including depression and anxiety, and (2) current evidence on the efficacy of psychological intervention in ICD patients.

Method: We carried out a narrative and meta-analytic review of the literature using general bibliographic database: MEDLINE, PsycINFO, and Social Science Citation Index.

Results: First, we found five studies investigating the relationship between ICD shock and depression, and six studies investigating the relationship between ICD shock and anxiety. However, there was no significant relationship between ICD shock and psychological status. In addition, a random effect meta-analysis of five randomized controlled trials produced overall effect sizes of $g = 0.17$ (95% CI = −0.09 to 0.43) for depression and $g = 0.38$ (95% CI = −0.10 to 0.86) for anxiety.

Conclusion: There was no significant relationship between ICD shock and psychological status including depression and anxiety, and no significant efficacy of psychological intervention in ICD patients. In the future studies, we should focus on confounding variable, and increase the methodological quality of the trial.

Letters to the Editor

For publication: Tiagabine in the discontinuation of long-term benzodiazepine use

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TOLERANCE, DEPENDENCE AND withdrawal symptoms are well-known complications of long-term benzodiazepine (BDZ) use, raising thorny problems in any attempt at their discontinuation. Among the scarce available pharmacological interventions, gradual rather than abrupt discontinuation of BDZ and use of the antiepileptic drug (AED) carbamazepine are the only successfully tested ones for their efficacy.[1] Thus, newer innovatory treatments are clearly desirable. The recent marketing of newer AED, especially of the Selective GABA-Reuptake-Inhibitors, such as tiagabine (TGB) might offer new therapeutic options to this end. However, to the best of our knowledge, no such studies or reports are as yet available. In the following, we report precisely on such a case.

This is the case of a 68-year-old female patient with a 15-year history of generalized anxiety disorder (GAD) and BDZ-dependence according to Diagnostic and Statistical Manual of Mental Disorders (text revision) criteria without any other psychiatric comorbidity, or medication. For the last five years, she was clearly abusing the BDZ bromazepam at a dosage of 75 mg/day, moreover with a notable tolerance to this drug, as attested by her high levels of anxiety despite its high dosage. This fact along with her resolution to address her BDZ-dependence motivated her hospitalization at our Department. On admission, the patient scored 39 on the Hamilton Anxiety Rating Scale (HARS). Her extensive medical and laboratory workup yielded no pathological findings. After obtaining the patient's written informed consent, we incrementally substituted TGB up to 15 mg/day for bromazepam within one week, each day replacing 10 mg of the latter with 2 mg of the former. Dizziness, headache and sedation were the only transient side-effects of TGB, subsiding within 10 days. On discharge, four weeks later, the patient's scores on the HARS had dropped to 22, a reduction rate by almost 44%.

With respect to its mechanism of action, we should note that TGB enhances GABAergic neurotransmission through its blockade of the GABA transporter I (GAT I). Besides its indication in epilepsy, TGB has been found safe and efficacious in various anxiety disorders including GAD, panic disorder, agoraphobia and post-traumatic stress disorder.[2] Moreover, in another recent study TGB has been found efficacious as monotherapy for major depressive disorder with anxiety.[3] However, we should mention the possible temporal delay of TGB – one week – to bring about its anxiolytic effects.[4] Although anecdotic and thus warranting replication in large and well-controlled studies, the findings of our case report suggest that TGB might be a promising new pharmacological agent in the treatment of BDZ dependence.

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Follow-up study of suicide attempters who were given crisis intervention during hospital stay: Pilot study

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FOR 10 CONSECUTIVE years the suicide rate in Japan has stayed at around 25 per 100 000, which is the highest among the developed countries.[1] Only a few follow-up studies, however, regarding suicide attempters are reported,[2,3] and both nationwide and community-based data are lacking in Japan.

The aim of the present study was to determine the prognosis of suicide attempters who were given crisis intervention during hospital stays, follows: (i) immediate psychiatric and psychosocial evaluation; (ii) psycho-education regarding the suicide behavior and psychiatric disease; and (iii) introduction of psychiatric treatment and social resource.

We targeted 144 patients who were admitted to the emergency department between 1 April 2005 and 31 March 2006 due to suicide attempts. Telephone interview was attempted twice, and the following questions were asked: (i) confirmation of survival; or (ii) cause of death. At the first interview (299 ± 100 days after discharge from the emergency department), 115 of 144 patients or their family responded to the interview. The suicide attempt rate was 4.3%, and the suicide rate was 2.6%. At the second interview (638 ± 97 days after

discharge), 83 patients or their family responded to the interview. The suicide attempt rate was 10.8%, and the suicide rate was 4.8%, and 61 of 144 patients (42.4%) were not traced. The reasons for lack of contact were as follows: 43 patients moved or changed their personal telephone numbers, and 18 patients refused to participate in this interview.

Suicide rate at the first interview was relatively low compared to other previous studies carried out in Finland and Sweden,[4,5] but whether this is due to the effect of crisis intervention is not clear because we could not trace 42.4% of the patients initially targeted. Therefore the main limitation in the present study is due to lack of information on the prognosis of the status of untraced patients.

The National Suicide Prevention Measure Outline was set in 2007. The need for investigation and research on suicide attempters is clearly noted in the outline. The emergency department is where medically serious suicide attempters are carried in, and suicide attempters account for 9% of all patients on annual average (2008).[6] The present study suggests that case management in the emergency department might be effective for preventing suicide. Further study, however, with more sophisticated methodology is required to establish a procedure to prevent suicide reattempt.

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Association between neuronal cell adhesion molecule (*NRCAM*) single nucleotide polymorphisms and schizophrenia in a Korean population

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WE EVALUATED POLYMORPHISMS of the neuronal cell adhesion molecule (*NRCAM*) gene for an association study with schizophrenia because this gene plays a crucial role in synapse formation and maturation of the nervous system.[1] Previous reports have shown the association between *NRCAM* and several psychiatric disorders.[2–4] In this study, the association between polymorphisms of *NRCAM* and schizophrenia in the Korean population was investigated.

A total of 285 schizophrenic patients (185 male, 42.8 ± 10.9 years [mean ± SD]; 100 female, 42.9 ± 10.8) and 302 control subjects (145 male, 39.9 ± 5.8; 157 female, 33.5 ± 6.2) were evaluated. All patients were diagnosed by two well-trained psychiatrists according to the Diagnostic Statistical Manual of Mental Disorders, 4th edition. Written informed consent was obtained from all subjects. The study was approved by the ethics review committee of the Medical Research Institute, Kyung Hee University Medical Center, Seoul, Republic of Korea. We searched for all single nucleotide polymorphisms (SNP) of the *NRCAM* gene region in human SNP databases (http://www.ensembl.org; http://www.ncbi.nlm.nih.gov/SNP; http://www.hapmap.org) and finally selected 13 SNP. The selected 13 SNP consisted of three exonic SNP (rs1802993, rs1043895, and rs1269634), six intronic SNP within an average distance of 300 bp from the nearest exon (rs2142325, rs6970656, rs722519, rs6954366, rs1990162, and rs917251), three promoter SNP (rs3763463, rs10235968, and rs6967368), and one SNP near the 3′ gene region (rs17155059). Multiple logistic regression models were used to calculate the odds ratio, 95% confidence interval, and corresponding *P*-values, controlling for age and gender as covariables, and to analyze associations between SNP and schizophrenia.

Of the 13 SNP examined, seven were polymorphic. The genotype distributions of five SNP (rs1990162, rs917251, rs3763463, rs10235968, and rs6967368) were in Hardy–Weinberg equilibrium (HWE; $P > 0.05$). Two SNP (rs1269634 and rs6970656) were not in HWE ($P < 0.05$). As a result, none of five SNP were associated with schizophrenia ($P > 0.05$; *P*-value was corrected using the Bonferroni method). Using the Gabriel method, two linkage disequilibrium blocks were

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Dopamine D_2 Receptor Gene Polymorphisms Are Associated with Suicide Attempt in the Japanese Population

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Key Words
Dopamine D_2 receptor · –141C Ins/Del · Suicide attempt · *Taq*IA · Polymorphism

Abstract

Background: Some reports have suggested the involvement of the D_2 dopaminergic function in the expression of suicidal behavior. Here, we examined associations between suicide attempts and two kinds of functional polymorphisms in the dopamine D_2 receptor (DRD2) gene, namely, *Taq*IA and –141C Ins/Del. ***Methods:*** Subjects included 120 suicide attempters and 123 unrelated volunteers. Those who attempted suicide were severely injured and were transferred to the emergency unit in our university hospital. To determine each genotype, we performed polymerase chain reaction and restriction fragment length polymorphism analyses. ***Results:*** We found significant differences in genotypic and allelic frequencies of –141C Ins/Del and *Taq*IA polymorphisms between suicide attempters and healthy controls (–141C Ins/Del, $p = 0.01$; *Taq*IA, $p = 0.036$). The Ins allele of –141C Ins/Del was significantly more frequent in suicide attempters ($p = 0.011$), as well as the A2 allele of *Taq*IA ($p = 0.017$). Haplotype analysis revealed no significant linkage disequilibrium between –141C Ins/Del and *Taq*IA polymorphisms ($D' = 0.226$, $r^2 = 0.016$, $p = 0.10$). ***Conclusions:*** These findings suggest that DRD2 gene polymorphisms may be involved in the biological susceptibility to suicide.

Introduction

Suicide is an important public health problem thought to be caused by different susceptibility factors. Several data from studies of family history suggest that transmitted factors have partial effects on suicidal behavior [1, 2]. Moreover, investigations on twins including adoption studies strongly support a genetic component in suicidal behavior, and rule out the effects of a shared environment [3–6]. Therefore, previous studies have pursued a possible genetic risk factor for suicide.

On the other hand, some studies have reported low cerebrospinal fluid (CSF) levels of the dopamine metabolite homovanillic acid (HVA) in depressed patients with a history of suicide attempts [7–10]. Bowden et al. [11] provided results supporting reduced dopamine turnover in the basal ganglia in depressed suicide completers by demonstrating decreased levels of dihydroxyphenylacetic acid, which is one of the metabolites of dopamine.

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These studies suggest an involvement of the D_2 dopaminergic function in the mechanisms of suicidal behavior.

A number of functional polymorphisms have been identified in the dopamine D_2 receptor (DRD2) gene to date [12]. Considering the possible association of DRD2 with the mechanisms of suicidal behavior, these polymorphisms can be considered as candidate genes for such behavior. Among these, the –141C Ins/Del polymorphism (rs1799732) in the promoter region was suggested to affect promoter activity, as shown by an expression study using human cells [13]. A previous study reported the possible association between –141C Del allele and attempted suicide in alcohol dependents [14]. *Taq*IA (rs1800497), which is located in the 3′ flanking region of DRD2 [15], is also associated with reduced DRD2 expression in vitro [16] and in vivo [17, 18], and with reduced D_2 receptor binding as measured by autoradiography [19]. This polymorphism is closely associated with personality traits [20], especially novelty seeking, which has been reported as a risk factor for suicide attempts [21, 22]. Therefore, these two polymorphisms are suspected to have a strong association with suicidal behavior.

In the present study, we screened for two kinds of DRD2 polymorphisms, namely, –141C Ins/Del and *Taq*IA, and assessed genetic associations with the occurrence of suicide attempt. To the best of our knowledge, this is the first association study between functional DRD2 polymorphisms and suicide attempters regardless of psychiatric disorders.

Materials and Methods

The study population consisted of 120 subjects (male = 45, female = 75) who attempted suicide and were admitted to the emergency unit of Yokohama City University Medical Center. The controls consisted of 123 unrelated healthy volunteers (male = 42, female = 81). All controls were recruited after informed consent was obtained, and were diagnosed as healthy using physician-conducted interviews and the Mini-International Neuropsychiatric Interview [23]. Subjects with current and chronic psychiatric disorders and a history of suicidal behavior were excluded.

All subjects were ethnically Japanese. The methods of suicide attempt were extracted from the patient's record, and divided into violent and nonviolent attempts according to the operational criteria of Yamada et al. [24] and subsequently analyzed. The violent suicide group was defined as follows: (1) mechanical ventilation was required for life support; (2) surgery was performed under general anesthesia; (3) the method of attempted suicide carried a high risk of death, specifically, hanging, gunshot, jumping from a high place, inhalation of gas, solvents, or other agricultural chemicals, thermal injury, or drowning.

Peripheral blood was drawn from suicide attempters and healthy controls, and leukocyte DNA was extracted for genotype determination. Polymerase chain reaction and restriction fragment length polymorphism analyses were performed to determine *Taq*IA genotypes according to Grandy et al. [15], and –141C Ins/Del genotypes according to Hori et al. [25]. Differences in the genotypic and allelic frequencies of the two gene polymorphisms between suicide attempters and control subjects were tested for significance using the χ^2 test and Fisher's exact test. The presence of Hardy-Weinberg equilibrium was determined using the χ^2 test. This analysis was performed with SPSS 11.0 for Windows (SPSS Japan, Tokyo). Pairwise linkage disequilibrium and estimated haplotypes were analyzed using Arlequin 2.000 [26]. We investigated the difference in genetic distribution in estimated haplotypes between suicide attempters and controls by the χ^2 test. In addition, logistic regression analysis was performed to evaluate simultaneously the possible associations between suicide attempts and independent variables (DRD2 genotypes, gender, and age). Probability differences of $p < 0.05$ were considered statistically significant.

Results

Table 1 shows the genotypic and allelic frequencies of two polymorphisms investigated in the suicide attempters and healthy controls. No deviation from Hardy-Weinberg equilibrium was observed in either the suicide attempters or healthy controls. We found a significant difference in genotypic distribution in the –141C Ins/Del polymorphism between the suicide attempters and healthy controls ($\chi^2 = 8.429$, d.f. = 2, p = 0.015). In addition, the frequencies of the –141C Ins allele were significantly higher in the suicide attempters than in the healthy controls (p = 0.011). On the other hand, we found no significant differences in the genotypic and allelic distribution between violent and nonviolent attempters (genotypic distribution, $\chi^2 = 1.827$, d.f. = 2, p = 0.401; allelic distribution, p = 0.295, detailed data not shown). The odds ratio (OR) for the suicide attempts associated with the Ins allele was 1.85 [95% confidence interval (CI), 1.16–2.94]. In addition, we found a significant difference in the genotypic distribution in *Taq*IA polymorphism between suicide attempters and healthy controls ($\chi^2 = 6.76$, d.f. = 2, p = 0.034). The frequency of the A2 allele of *Taq*IA was significantly higher in suicide attempters than in healthy controls (p = 0.017), and the OR for the suicide attempts associated with the A2 allele was 1.56 (95% CI, 1.09–2.25). Similarly, as shown in table 2, logistic regression analyses showed a significant association between suicide attempts and the –141C Ins/Del genotypes (p = 0.014; OR, 1.95; 95% CI, 1.15–3.32) and *Taq*IA genotypes (p = 0.014; OR, 1.58; 95% CI, 1.06–2.35). However, we found no significant genetic and allelic frequency differences between violent and nonviolent attempters (genotypic distribution, $\chi^2 = 0.520$, d.f. = 2, p = 0.771; allelic distribution, p = 0.762, detailed data not shown).

Pairwise linkage disequilibrium was also analyzed and no significant linkage disequilibrium was detected between –141C Ins/Del and *Taq*IA polymorphisms (D′ = 0.226, $r^2 = 0.016$, p = 0.10). As shown in table 3, no significant difference was found in the estimated haplotype frequencies between suicide attempts and controls ($\chi^2 = 12.12$, d.f. = 3, p = 0.07). Using SPSS Sample Power version 2.00, we estimated that the statistical power of our study was 64–74%.

Table 1. Genotype distributions and allele frequencies of polymorphisms in the DRD2 gene: –141C Ins/Del and *Taq*IA polymorphisms

	All suicide attempters (n = 120)	Controls (n = 123)	p
–141C Ins/Del			
Genotypes			
Ins/Ins	86 (71.7)	66 (53.7)	0.015*
Ins/Del	33 (27.5)	55 (44.7)	
Del/Del	1 (0.8)	2 (1.6)	
Alleles			
Ins	205 (85.4)	187 (76.0)	0.011*
Del	35 (14.6)	59 (24.0)	
*Taq*IA			
Genotypes			
A1/A1	13 (10.8)	27 (22.0)	0.034*
A1/A2	63 (52.5)	64 (52.0)	
A2/A2	44 (36.7)	32 (26.0)	
Alleles			
A1	89 (36.5)	118 (48.0)	0.017*
A2	151 (63.5)	128 (52.0)	

Figures in parentheses indicate percentages. p = Significance probability between all suicide attempters and controls; * = significant difference between suicide attempters and controls.

Table 2. Logistic regression analysis of independent variables of suicide attempters

Independent variables	Partial regression coefficients	p	OR (95% CI)
Gender	0.033	0.001	1.033 (1.013–1.053)
Age	–0.141	0.618	0.869 (0.500–1.511)
*Taq*IA genotype	0.455	0.026	1.576 (1.056–2.350)
–141C Ins/Del	0.668	0.014	1.950 (1.147–3.317)

Table 3. Estimated haplotype distribution of the DRD2 gene polymorphisms between suicide attempters and controls

	Suicide attempters (n = 120)	Controls (n = 123)
A1-Ins	0.272	0.370
A1-Del	0.107	0.098
A2-Ins	0.582	0.395
A2-Del	0.039	0.138

p = 0.07.

Discussion

The role of the dopaminergic system in the mechanisms of suicidal behavior has not yet been fully clarified. Several studies have reported low CSF HVA levels in depressed patients with a history of suicide attempts compared with healthy controls [7–10]. Low CSF levels of HVA could be a more reliable index of suicidal behavior than low CSF 5-hydroxyindoleacetic acid [10]. Pitchot et al. [27] suggested a smaller growth hormone response to apomorphine, which is a dopaminergic agonist, in depressed patients with a history of suicide attempts compared with nonattempters. This study indicates a specific role for the dopamine system, particularly DRD2, in the pathogenesis of suicide. Therefore, functional polymorphisms of the DRD2 gene, which affect the DRD2 function, should be of great interest in investigating vulnerability to suicide attempts.

In the present study, we performed screening for two functional DRD2 polymorphisms, and assessed the relationship between suicide attempts and these polymorphisms. We found significant differences in genotypic and allelic frequencies of the –141C Ins/Del polymorphism between suicide attempters and healthy controls. The frequencies of the –141C Ins allele were significantly higher in the suicide attempters. Jönsson et al. [17] demonstrated by positron emission tomography that the striatal DRD2 density in healthy subjects with the Del allele was higher than that in those without the Del allele. In view of the functional relationship of DRD2 –141C Ins/Del polymorphisms to DRD2 activity, our results suggest that the –141C Ins variant, which reduces DRD2 density, plays an important role as a risk factor for suicide attempts.

On the other hand, we did not observe any significant differences between high and low lethality of suicide attempts. Some previous studies showed differences in the concentrations of CSF 5-hydroxyindoleacetic acid and HVA between the two groups [28–30]; however, the results of these studies were inconsistent. Pitchot et al. [31, 32] reported that the growth hormone peak responses to apomorphine showed no difference between depressed patients with a history of high-lethal suicide attempt and patients with a history of low-lethal suicide attempt. Our result indicates that violent and nonviolent attempters may have a similar pathogenesis, particularly in the DRD2 function influenced by gene polymorphisms.

We also found a significant difference in the genotypic distribution associated with *Taq*IA polymorphism between suicide attempters and healthy controls. The frequencies of the *Taq*IA A2 allele were significantly higher in the suicide attempters. In previous reports, *Taq*IA polymorphism was suggested to be associated with reduced DRD2 expression in vitro [33] and in vivo [17, 19]. However, Pohjalainen et al. [18] and Laruelle et al. [34] showed no association between *Taq*IA polymorphism and D_2 dopamine binding potential in a positron emission tomography study. The unreplicated result regarding human striatal DRD2 density remains of great interest. However, the results of receptor function studies in vivo have been inconsistent to date, and we could not specifically elucidate the pathogenetic mechanism of suicide in the present study. Since this is the first association study between suicide attempters and *Taq*IA polymorphisms, further studies using larger samples are needed to confirm the present results.

From our findings, the DRD2 –141C Ins/Del and *Taq*IA gene polymorphisms are suggested to affect the pathogenesis of suicide. However, this study has some limitations. First, we examined suicide attempters and not suicide completers. There are some reports suggesting differences between these two subject groups [35]. Previous reports, however, have also pointed out biological similarities between suicide completers and suicide attempters [30]; therefore, we speculated that genetic studies on our subjects who attempted suicide would reflect the possible mechanisms underlying suicidal behavior. Second, we were unable to carry out association studies between psychiatric disorders and suicide attempt because the sample number was too small. Moreover, although it is known that a family history of suicide increases suicide risk [36], we did not investigate the association regarding family history of psychiatric disorders for all 2 degrees of relationship. In the present study, we cannot completely exclude the possibility that the psychiatric disorders and family suicidal histories of the subjects might have affected our results.

Third, our total sample size was relatively small. Replication studies using larger samples are required to specifically clarify the possible effects of –141C Ins/Del and *Taq*IA polymorphisms of the DRD2 gene on the pathogenesis of suicide.

Conclusion

Our findings indicate that –141C Ins/Del and *Taq*IA polymorphisms of the DRD2 gene are involved in the suicidal behavior of attempters. A more conclusive study employing a substantially larger sample may be required to verify the associations between the two polymorphisms and suicide attempts. Moreover, we believe that the gene polymorphisms and physiological processes involved in suicide attempts involve many complex factors. Another approach to fully clarify the above-mentioned associations possibly involves a study of the combination of other genetic factors, such as serotonin-related genes, which has the potential to elucidate genetic risk factors involved in suicide.

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Characteristics of suicide attempters with family history of suicide attempt: a retrospective chart review

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Abstract

Background: Family history of suicide attempt is one of the risks of suicide. We aimed at exploring the characteristics of Japanese suicide attempters with and without a family history of suicide attempt.

Methods: Suicide attempters admitted to an urban emergency department from 2003 to 2008 were interviewed by two attending psychiatrists on items concerning family history of suicide attempt and other sociodemographic and clinical information. Subjects were divided into two groups based on the presence or absence of a family history of suicide attempt, and differences between the two groups were subsequently analyzed.

Results: Out of the 469 suicide attempters, 70 (14.9%) had a family history of suicide attempt. A significantly higher rate of suicide motive connected with family relations (odds ratio 2.21, confidence interval 1.18–4.17, $p < .05$) as well as a significantly higher rate of deliberate self-harm (odds ratio 2.51, confidence interval 1.38–4.57, $p < .05$) were observed in patients with a family history of suicide compared to those without such history. No significant differences were observed in other items investigated.

Conclusion: The present study has revealed the characteristics of suicide attempters with a family history of suicide attempt. Further understanding of the situation of such individuals is expected to lead to better treatment provision and outcomes, and family function might be a suitable focus in their treatment.

Background

Suicide is a complicated phenomenon, and various factors are implicated in its pathogenesis [1]. Suicide risk has been reported to be associated with single marital status [2], indebtedness, unemployment [3], lower social class, male gender [4], somatic illness and psychiatric disorder [5], and history of a suicide attempt [6,7]. In addition to these risk factors, there is growing recognition that suicide and suicidal behavior (any deliberate action with potentially life-threatening consequences) tend to be familial [8-12]. Familial suicide behavior may be mediated by the transmission of endophenotypes, such as impulsivity. Environmental conditions may also result in familial transmission [13,14]. In addition, parental impulsive aggression predisposes individuals to family instability and abuse, which further increases the risk of suicidal behavior in offspring [8,15,16]. Suicidal behavior is known to aggregate in families, and both genetic and non-genetic factors responsible for familial transmission of suicidal behavior should be discernible among suicide attempters and may be suitable targets for preventive therapeutic intervention [9].

In this study, we examined the suicidal behavior and detailed sociodemographic data of suicide attempters with and without a family history of suicide attempt in order to explore our main hypothesis that suicide attempters with a family history of suicide attempt have some characteristics related to family environmental conditions. A better understanding of the situation of suicide attempters with such a history could prove useful in the provision of patient care.

Methods

The present study was performed at the Advanced Critical Care Medical Center, Yokohama City University Medical Center, which is located in Yokohama, a mega city with a population of about 3.6 million people. The center receives all patients with potentially fatal conditions from the southern part of the city, and suicide attempters account for on average 13.0% (April 1, 2003 – March 31, 2008) of all admitted patients.

Procedure

Between April 1, 2003 and March 31, 2008, a total of 686 suicide attempters were admitted to the center. Attempted suicide was defined as any intentional self-inflicted harm alongside suicidal ideation. Among these, 102 patients who committed suicide were excluded from the study since we could not confirm suicidal intent or obtain sufficient research information as their identities were unknown when in our care. Of the remaining 584 patients who attempted suicide, 38.2% ($n = 223$) were male and 61.8% ($n = 361$) were female, with an age ranged of 14 to 88 years and a mean of 38.0 years, standard deviation 15.9 years ($M = 41.1$, $SD = 15.9$ years for males; $M = 36.2$, $SD = 15.5$ years for females). Psychiatric diagnosis was made according to DSM-IV criteria [17] by agreement of two psychiatrists. The most common axis I diagnosis of DSM-IV was major depressive disorder (23.1%), followed by adjustment disorder (19.5%), schizophrenia (15.4%), and substance use disorder (10.4%). The most common axis II diagnosis of DSM-IV was personality disorder (32.0%), followed by mental retardation (1.2%). The breakdown of the axis II diagnosis of DSM-IV was borderline personality disorder (55%), personality disorder not otherwise specified (33%), antisocial personality disorder (9%), and others.

Patients were interviewed by two psychiatrists on the following items: 1) family history of suicide attempt, 2) living status, 3) education, 4) previous psychiatric history, 5) somatic complications, 6) method of suicide attempt, 7) history of suicide attempt, 8) history of deliberate self-harm (no suicidal ideation), and 9) motive of suicide attempt. Regarding suicide motives, patients selected the motive that corresponded most closely to their situation from the following 7 options: family relations, human relations (work place or school), male-female relationships, health issues, financial situation, work environment, or other reason.

Subjects were divided into two groups based on the presence or absence of a family history of suicide attempt, and the differences between the two groups were subsequently analyzed. We counted every suicide attempter among a first-degree relative and grandparent. No suicides among children were reported by the patients in our sample. The flow of the patients through this study is presented in Figure 1.

Statistical analyses

Statistical analyses were conducted using SPSS for Windows version 16.0. The chi-square test and t-test were used to compare those who reported a family history of suicide attempt and those who did not. The chi-square test was used to explore the differences between those with and without a family history of suicide in relation to gender, living status, and education. The t-test was used to compare the differences between those with and without a family history of suicide in relation to age. Further, logistic regression analysis was performed to determine differences between those with and without a family history of suicide in relation to previous psychiatry history, somatic complications, method of suicide attempt, history of suicide attempt, history of deliberate self-harm, and motive of suicide attempt. In the logistic regression model, we used age, gender, and living status as adjustment variables. A probability level of $p < .05$ was considered statistically significant.

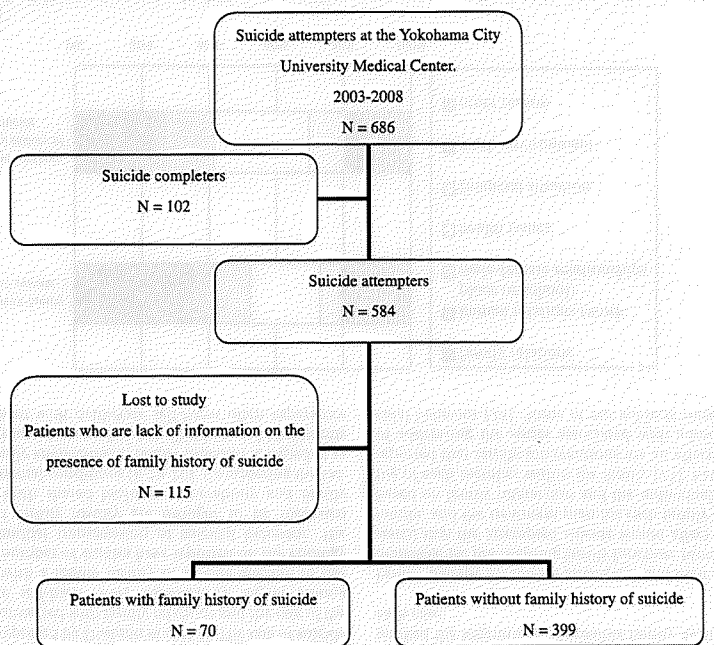

Figure 1
Flow of subjects through the study.

Ethics

The study protocol was approved by the ethics committee of Yokohama City University School of Medicine, and conforms to the provisions of the Declaration of Helsinki in 1995. We obtained informed consent from all participants and their anonymity was preserved.

Results

Among the original sample of 584 patients, data from 115 patients (20%) were not submitted due to lack of information regarding the presence of a family history of suicide attempt. Information was lacking either because hospitalization in the emergency department was too short to obtain all information or in the case that a patient had consciousness disturbance due to head injury. Nevertheless, these untraced 115 patients did not differ significantly from the traced patients in terms of either gender or age ($p > .05$). Finally, data from 469 patients were analyzed and the results are presented below. The sample was composed of 173 (36.9%) males and 269 (63.1%) females, with an age range of 14 to 88 years and a mean of 38.1 years, standard deviation of 15.7 years ($M = 40.6$, $SD = 15.7$ years for males; $M = 36.7$, $SD = 15.5$ years for females).

Analysis revealed that 70 (14.9%) had a family history of suicide attempt and 399 (85.1%) had no such history. Sociodemographic and clinical characteristics when divided into presence or absence of a family history of suicide attempt are shown in Table 1. Figure 2 shows the breakdown of motive of suicide attempt by percentage, where the most common motive among patients with a

family history of suicide attempt was revealed to be family relations (34.9%), followed by health issues (18.6%), and other reason (17.1%). For patients without a family history of suicide attempt, the most common motive of suicide attempt was health issues (28.3%), followed by family relations (22.4%), and other reason (19.0%). Thus, patients with a family history of suicide attempt showed a significantly higher rate of suicide motive connected with family relations than those without such history, with an adjusted odds ratio of 2.21 (1.18 to 4.17, $p < .05$, adjusted for age, sex, and living status), as well as a significantly higher rate of deliberate self-harm (DSH) (50% versus 34.0%, respectively), with an adjusted odds ratio of 2.51 (1.38 to 4.57, $p < .05$, adjusted for age and sex) (Table 2). Aside from these two characteristics, no significant differences between the two patient groups were observed for any other items investigated.

Discussion

This study was performed to determine whether suicide attempters with a family history of suicide attempt showed characteristics different from those without such history. Of note, this is the first study to focus on motives

Table 1: Sociodemographic and clinical characteristics of suicide attempters, and presence/absence of family history of suicide

	Total *n* (%)	Patients with family history of suicide *n* (%)	Patients without family history of suicide *n* (%)
Living status (*n* = 453)			
Alone	100 (22.1)	14 (21.2)	86 (22.2)
Together	353 (77.9)	52 (78.8)	301 (77.8)
Education (*n* = 451)			
Compulsory education*	125 (27.7)	23 (33.8)	102 (26.6)
High school education and over	326 (72.3)	45 (66.2)	281 (73.4)
Previous psychiatric history (*n* = 467)	329 (70.4)	53 (76.8)	276 (69.3)
Somatic complications (*n* = 469)			
Permanent damage	12 (25.6)	2 (2.9)	10 (2.5)
No permanent damage			
Require in-patient treatment	45 (9.6)	4 (5.7)	41 (10.3)
Require out- patient treatment	84 (17.9)	15 (21.4)	69 (17.3)
Without physical complications	328 (69.9)	49 (70.0)	279 (69.9)
Method of suicide attempt (*n* = 469)			
Drug overdose	244 (52.0)	37 (52.9)	207 (51.9)
Laceration	71 (15.1)	12 (17.1)	59 (14.8)
Jumping from high place	58 (12.4)	9 (12.9)	49 (12.3)
Poisoning	44 (9.4)	8 (11.4)	36 (9.0)
Burning	14 (3.0)	0 (0)	14 (3.5)
Traffic death	13 (2.8)	1 (1.4)	12 (3.0)
Hanging	18 (0.2)	3 (4.3)	15 (3.8)
Drowning	4 (0.9)	0 (0)	4 (1.0)
Other	3 (0.6)	0 (0)	3 (0.8)
Previous suicide attempt (*n* = 443)	206 (44.8)	38 (55.1)	168 (43.0)
Previous deliberate self-harm (*n* = 460)	161 (36.3)	33 (50.0)	128 (34.0)
Motive of suicide attempt (*n* = 416)			
Family relations	101 (24.3)	22 (34.9)	79 (22.4)
Human relations (work place or school)	19 (4.6)	4 (6.3)	15 (4.2)
Male-female relationships	59 (14.2)	7 (11.1)	52 (14.7)
Health issues	113 (27.2)	13 (20.6)	100 (28.3)
Financial situation	42 (10.1)	4 (6.3)	38 (10.8)
Work environment	19 (4.6)	1 (1.6)	18 (5.1)
Other reason	63 (15.1)	12 (19.0)	51 (14.4)

* Compulsory education lasts for 9 years; statutory schooling ages are between 6 and 15 years in Japan.

Table 2: Results of examining the difference between patients with and without family history of suicide (N = 469)

	Adjusted OR (CI 95%)	p value
Deliberate self-harm†	2.51 (1.38–4.57)*	0.003
Motive of suicide attempt connected with family relations‡	2.21 (1.18–4.17)**	0.013

Note. * Odds ratio (OR) adjusted for sex and age.
** OR adjusted for sex, age, and living state.
† Nine of the 469 patients were excluded from the analysis due to insufficient data.
‡ Fifty-three of the 469 patients were excluded from the analysis due to insufficient data.
Confidence interval = CI.

of suicide attempt in suicide attempters with a family history of suicide.

In this study, 14.9% of the suicide attempters at our emergency department had a family history of suicide attempt, which is similar in frequency (13.2%) to that among suicide attempters with a family history of suicide attempt recently reported by Diaconu et al [15]. The rate of suicide motive connected with family relations and the rate of the deliberate self-harm were significantly higher among patients with a family history of suicide attempt in our study. A number of studies have reported on the etiology of the familial transmission of suicidal behavior. The effects of family history are thought to be mediated through both shared biologic vulnerability and family environmental conditions [8,18-20]. Considering the factor of family environment, family function is regarded as one of the key elements [13,21]. Children and adolescents who present with deliberate self-harm often experience major life problems, especially in relationships with family members [22,23]. Family discord has consistently been shown to be both a correlate and predictor of adolescent suicidal behavior [24]. Our finding is not in conflict with these previous studies. While family dysfunction might be related to the cause of suicide, we were not aware of the details of their "family relations" motive or of whether it marked the beginnings of possible family dysfunction in each case.

Family therapy for suicide attempters and their families is beneficial for maintaining family function. Morrison et al. stated that the attempted suicide would affect the entire family, and the treatment plan for each family should be based on family interaction and the individual functioning of each member within the family [25]. Kerfoot et al. reported that family interventions are an effective means of addressing the issues associated with adolescent suicidal behavior [26]. Some of our subjects were bereaved

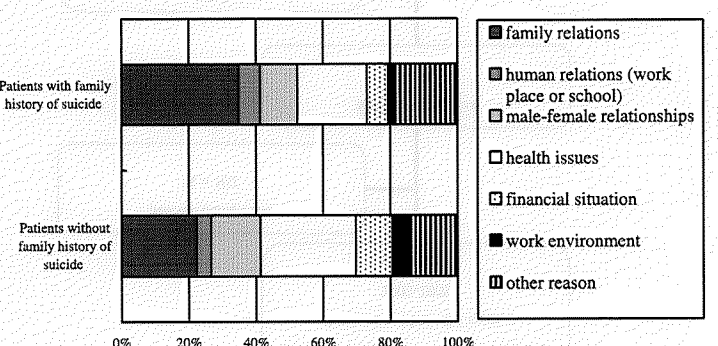

Figure 2
Classified subitems of motive of suicide attempt. The most common motive of suicide attempt concerned family relations (34.9%) in patients with a family history of suicide attempt.

due to family history of suicide, and in the case of bereavement, previous studies have indicated the effectiveness of intervention and social support to reduce distress and suicidal ideation [27-29]. In addition, there is also a pressing need for studies that ask those with a family history of suicide attempt themselves what has been of help or what they feel so that interventions can be designed to strengthen the natural coping efforts of families [30]. Reducing the stigma of suicidal behavior and increasing awareness of the psychological distress of individuals who experience suicidal behavior of their family will make it much easier for them to access social support. In Japan, where the increasing number of suicides is of grave concern, the National Suicide Prevention Measure Outline established in 2007 stated the need to provide care and social resources for both bereaved families and families of suicide attempters [31].

We recognize some limitations of our study. First, we did not conduct structured interviews with suicide attempters to diagnose psychiatric disorder. Hospitalization in our emergency department is too short to perform structured interviews for patients. Instead, psychiatric diagnosis was made on the consensus of two attending psychiatrists. The second limitation is that the situation of cohabitation at the time when a family member attempted suicide was unclear. The third limitation is that some of the suicide attempters may have been unaware of a family history of suicide attempt.

Conclusion

In the emergency department, 14.9% of suicide attempters had a family history of suicide attempt. We observed significantly higher rates of suicide motive connected with family relations and of deliberate self-harm in suicide attempters with a family history of suicide attempt than in those without such history. These findings indicate that care for the suicide attempters should take into consideration a family history of suicide. Replication of these findings in future studies that perform more extensive investigation is warranted.

Abbreviations

DSM: The Diagnostic and Statistical Manual of Mental Disorders.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MN, RS, YI contributed to data collection. MN, CK, TY, HH, TO, YH wrote the analysis plan. MN and SM conducted the statistical analysis. CK discussed the ideas in paper and contributed to manuscript preparation. All authors contributed to the interpretation of the results and the final manuscripts.

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A randomized controlled multicenter trial of post-suicide attempt case management for the prevention of further attempts in Japan (ACTION-J)

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Abstract

Background: A previous suicide attempt is a potent risk factor for suicide later on. Crisis intervention, psychiatric and psychosocial evaluation at emergency medical facilities, and follow-up care for suicide attempters are considered important components for suicide prevention. The Japanese Multimodal Intervention Trials for Suicide Prevention (J-MISP) includes a randomized, controlled, multicenter trial of post-suicide attempt case management for the prevention of further attempts (ACTION-J) to address the continuing increase in suicides in Japan. The primary aim of ACTION-J is to examine the effectiveness of an extensive intervention for suicide attempters in prevention of recurrent suicidal behavior, as compared with standard intervention. This paper describes the rationale and protocol of the ACTION-J trial.

Methods/Design: In this clinical trial, case management intervention will be provided at 19 emergency medical facilities in Japan. After crisis intervention including psychiatric evaluation, psychosocial assessment, and psychological education, subjects will be randomly assigned to either a group receiving continuous case management or a control group receiving standard care. Suicidal ideation, depressive symptoms, and general health condition will be evaluated as secondary

measures. The intervention was initiated in July 2006. By December, 2009, 842 subjects will be randomized. Subject follow-up will continue for 1.5 to 5 years.

Discussion: Suicide is a complex phenomenon that encompasses multiple factors. Case management by multi-sector collaboration is needed. ACTION-J may provide valuable information on suicide attempters and may develop effective case management to reduce future risk for suicide attempters.

Trial registration: UMIN Clinical Trials Registry number, UMIN000000444. ClinicalTrials.gov number, NCT00736918.

Background

A history of suicide attempt as a risk factor for suicide

Based on studies in Europe, North America, and Australasia, a previous suicide attempt is a key risk factor for completed suicide [1-3]. After a follow-up period of 1 year, 12% to 15% of repetitions of cases of self-harm or suicide attempt are non-fatal, whereas 0.8% to 2.6% are fatal. After a follow-up period of 9 years, 3% to 12% ended in completed suicide [4]. Given these statistics, intervention for suicide attempters is an important element to prevent suicide.

Recent increase in suicides in Japan

For approximately two decades (from 1978 to 1997), the suicide rate in Japan has been between 17.0 and 21.0 per 100,000 people. In 1997, 24,931 suicides were reported in Japan. In 1998, a dramatic 1.35-fold increase in the number of suicides in Japan occurred, as 32,863 suicides were reported. Since 1998, suicide rates in Japan have been between 25.2 and 27.0 per 100,000 people. For 11 years, the annual number of suicides in Japan has remained over 30,000 [5]. According to statistics from the World Health Organization (WHO) compiled in 2007 concerning worldwide suicide rates, the suicide rate in Japan was the eighth highest in the world [6].

Recent preventive measures against suicide in Japan

"The Declaration of Suicide Prevention" was issued in 2002 in Japan by the Advisory Panel on Strategy for Suicide Prevention. Since 2002, various measures associated with suicide prevention have been implemented, such as publication of suicide prevention manuals for the work place and medical practitioners. However, the number of suicides has not yet declined significantly. Therefore, in 2005, an intensive deliberation on suicide prevention was held by the Health, Labour, and Welfare Committee in the House of Councillors, and "The Resolution on Urgent and Effective Promotion of Comprehensive Strategies for Suicide" was passed in July 2005.

Also in 2005, two research projects (Japanese Multimodal Intervention Trials for Suicide Prevention: J-MISP [7]) funded by The Japanese Ministry of Health, Labor and Welfare (JMHLW), were launched to develop effective strategies to prevent suicide. J-MISP consists of a community intervention trial of a multimodal suicide prevention program (NOCOMIT) [8] and a randomized controlled multicenter trial of post-suicide attempt case management to prevent further attempts (ACTION-J).

Review of strategies of intervention for suicide attempters

Various studies on intervention for suicide attempters as well as systematic reviews of these studies have been reported [9-14]. Few randomized controlled trials that focused on intervention methods showed a significant decrease in the repetition rate for attempted suicide. Van Herringen and colleagues investigated the effects of various strategies to increase compliance with referrals for outpatient aftercare [9]. Twenty-one of 196 patients (10.7%) in the experimental group and 34 of 195 patients (17.4%) in the control group repeated their suicidal behavior. The odds ratio was 0.57 (95% CI: 0.32 to 1.02).

A summary of 5 studies comparing cognitive behavioral therapy with standard aftercare demonstrated an odds ratio of 0.70 (confidence interval, 0.45 to 1.11), indicating the effects on suicide prevention. A summary of 6 studies involving intensive outreach, brief inpatient treatment, and nursing care, as compared with standard care, produced the odds ratio of 0.83 (CI: 0.61 to 1.14) [12].

Small sample sizes in the primary studies selected for the systematic review resulted in a wide range of confidence intervals for the odds ratios. Fewer than 600 subjects in both the experimental and control groups participated in the 5 studies to evaluate cognitive behavioral therapy and the 6 studies to investigate the effects of outreach programs. Thus, the total number of subjects in these studies was under 1,200. In addition, the follow-up period after enrollment was only 6 to 12 months. Hawton and colleagues [11] and Gaynes and colleagues [13], noting the limitations of studies with too few subjects and too short a study period, emphasized the need for large trials at

multiple sites in order to determine the benefits of interventions.

Overall scheme of ACTION-J

The act of suicide is complex. Findings from previous psychological autopsy studies in other countries indicate that more than 80% of patients who completed suicide could be diagnosed with a psychiatric disorder [15,16]. Over 80% of highly lethal (incomplete) suicide attempters taken to emergency medical centers in Japan were diagnosed with axis I psychiatric disorders, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [17]. Proper psychiatric assessment and treatment of suicide attempters may be critical to suicide prevention.

Based on these findings, we chose to utilize emergency medical facilities as trial sites and designed an intervention trial involving close collaboration between emergency medicine and psychiatric medicine for management of suicide attempters with psychiatric disorders. We planned a large-scale, multisite study in Japan.

In this trial, case management is employed as an intervention method. Case management provides multi-dimensional and comprehensive care that has not been studied in previous research, and includes psychological education, follow-ups to increase compliance with referrals for outpatient treatment, individualized casework including coordination of use of social resources, and information technology-based services. Prevention of further suicide attempts will be compared between subjects in the experimental group who receive the specialized, case management care and subjects in the control group who receive standard care.

Objective of this study

The objective of this study is to examine the effectiveness of a trial intervention to prevent recurrent suicidal behavior by suicide attempters in Japan, as compared with a control intervention. It is expected that the case management administered in this study will be effective to prevent recurrence of suicide attempts.

Methods/Design

ACTION-J is an open, randomized, controlled, multicenter study which examines the effectiveness of a trial intervention for suicide attempters in Japan. The trial intervention involves the implementation of case management for suicide attempters transported and admitted to emergency medical facilities. The task schedule is presented in Table 1.

Organization

JMHLW selected the Japan Foundation for Neuroscience and Mental Health (JFNMH) as the primary institution responsible for J-MISP, in close collaboration with the National Center of Neurology and Psychiatry. The J-MISP administration office in JFNMH will organize overall administrative procedures regarding the operations of the ACTION-J study group. The office will also establish and operate the steering committee, central research ethics

Table 1: Task schedule

	during admission	at discharge	1 w after discharge	4 w	8 w	12 w	6 m	12 m	18 m	24 m	30 m	36 m	42 m	Interim/ Final analysis
Psychiatric diagnosis	◎													
Psychoeducation 1*	◎													
Informed consent	◎													
Enrollment/ randomization	◎													
Input data at time of discharge		◎												
Case management (Psychoeducation 2**, others)	○		○	○	○	○	○	○	○	○	○	○	○	
Psychiatric evaluation	◎						◎		◎		◎		◎	
Event	Input content of the event (ie, recurrent suicidal behavior, adverse event) into the web system as occasions require													
Participant survival (or cause of death of the participant)														◎
Actions to critical situations	In both groups during the study as occasions require													
Reports of a serious adverse event	Prompt report to the director of the hospital and the study group management office in both groups as occasions require													

◎ : Implemented in both groups; ○ : Implemented only in experimental intervention group
*: Psychoeducation Program I to all participants in both groups
**: Psychoeducation Program II to their family members during hospitalization in the experimental group
w: week, m: month

committee, study evaluation committee, and study progress control committee.

The ACTION-J study group will include 19 participating hospitals in Japan. The study group will comprise the following: the study group management office, each participating hospital, the steering committee, the principal statistician, the independent statistician, the intervention program committee, the event review committee, and the data management center for technical support.

Each participating hospital will have psychiatrists, emergency department physicians, case managers, and other personnel. In addition, one coordinator, either a psychiatrist or an emergency physician, will be assigned to each participating hospital. Other participating researchers in this study include experts in suicide prevention, nurses, clinical psychologists, psychiatric social workers, biostatisticians, epidemiologists, and coordinators of the data management center.

Subjects

Subjects will include individuals who are admitted to emergency medical facilities in Japan, are evaluated by an emergency physician or a psychiatrist in the emergency department, and are diagnosed as having made a suicide attempt. Subjects must also meet the following inclusion criteria:

Inclusion criteria

1) Subject is over 20 years old.

2) Subject has been diagnosed with a psychiatric disorder classified into DSM-IV axis I.

3) Subject has had suicidal intentions confirmed at least twice using the Suicide Intent Scale [18].

4) Subject is able to understand the description of the study and provide informed consent.

5) During hospitalization, subject is able to attend an interview and the *Psychoeducation Program I* (see *Intervention* section), which will be required before enrollment in the study.

6) Subject is able to visit the participating hospital regularly for evaluations and case management and be contacted directly from the hospital on a regular basis.

Exclusion criterion

1) Individual has a primary diagnosis that is not classified into DSM-IV axis I.

Estimation of sample size

The total sample size is 842 participants, including 421 participants in each of the two treatment groups. Calculation of the desired sample size was based on the following rationale. According to a study of suicidal individuals transported to psychiatric emergency facilities in Japan, the annual incidence rate of events (including death) was set at 15% in the control group [19]. The target reduction in recurrent suicidal behavior in the trial intervention group was set at approximately 30%; the annual incidence rate of events (including death) in the intervention group was estimated to be 10.5% [20].

Based on this estimation, we calculated the sample size using the method of Shoenfeld and Richter, in order to confirm that the intervention group is superior, with a significance level of 2.5% for the one-sided test and a power of 90%, dependent on a 3.5-year-enrollment period and a 1.5-year follow-up period after enrollment. Given these assumptions, the desired number of participants per group was calculated to be 518, and number of events was expected to be 296. Sample size was set to increase the likelihood that the expected number of events (≥ 90% if no participant is lost to follow-up) would be observed during the study period.

Informed consent

Participants will be patients admitted to the participating hospitals on an emergency basis, those who meet the inclusion criteria, and who provide informed consent to participate in this study.

Enrollment

Participant enrollment will be based on the following procedural outline (Figure 1). Any physician in an emergency facility will contact a psychiatrist when suspecting that a patient has made a suicide attempt. The psychiatrist will collect information and make a psychiatric diagnosis when examining the patient. At this point, the patient's suicidal intention will be confirmed (first check for suicidal intention). The investigator will confirm that the patient has not yet participated in this trial (i.e., that this event is not a repetition of suicidal behavior of a participant already enrolled in this trial) and will determine whether the patient is eligible to participate in this study by reviewing the inclusion and exclusion criteria. The investigator will explain this study, as well as the *Psychoeducation Program I* (see the description in the *Intervention section*), to a patient who is confirmed to have suicidal intentions and obtain patient consent. Next, a practitioner in charge of the psychoeducation program will provide the *Psychoeducation Program I* to the patient.

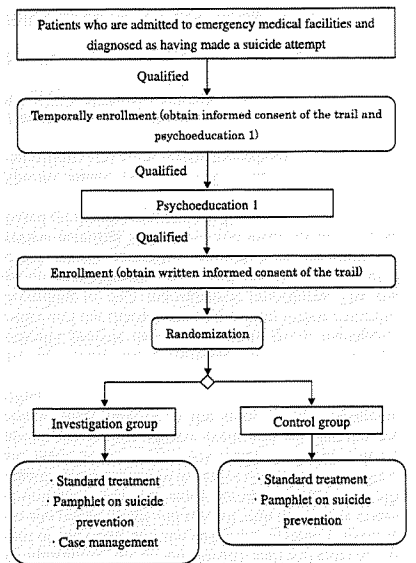

Figure 1
Flow diagram of the study.

The investigator will again confirm the suicidal intentions of a patient who is deemed eligible to participate in the study. After the patient completes the *Psychoeducation Program I*, the investigator will reconfirm the suicidal intentions of a patient who is deemed eligible to participate in the study (second check for suicidal intention). The investigator will obtain written consent from the patient to participate in this study. On-site research staff at the participating hospital will collect data from the participant at the time of enrollment and enter the information via a web input system to receive a random assignment. The participant will be informed about his/her assigned group and the subsequent schedule within 1 week (by the time of the first interventional treatment).

Randomization

Using the minimization method, participants will be randomly assigned to either the intervention group or control group. Central assignment involving an Internet-based assignment system will be performed.

Participants will be randomly assigned to one of the two groups according to the following factors:

1) Hospital

2) Gender

3) Age (< 40 or ≥ 40 years)

4) History of suicide attempts

Intervention

All participants will attend the semi-structured *Psychoeducation Program I*, which will involve a discussion of psychological changes leading to suicide, risk factors for suicide and the relationship to psychiatric disorders; introduce stress management; demonstrate the usefulness of psychological and social support; and make patients aware of social resources. After randomization, the following interventions will be carried out in the respective groups (Table 1).

Case management intervention in the experimental group

Case managers will periodically contact participants assigned to the experimental intervention group (on the 1st, 4th, 8th, and 12th week and the 6th month after the day of written consent, and every 6 months thereafter until the end of the study). Case managers will inform participants about the date of their scheduled interviews in advance, via e-mail or regular mail. E-mail messages for participants will be prepared with the e-mail form on the input system and sent via the dedicated e-mail address for this study; the dedicated e-mail address does not permit any replies. Regular mail will be sent by participating hospitals, and words such as suicide will not be printed on the envelopes.

In principle, case management should be accomplished through direct dialogue (face-to-face interviews), where a telephone conversation is the next best option. Interviews should be conducted at participating hospitals. If case managers cannot reach participants, case managers will approach participant family members who have given their consent to be contacted in advance.

The interview scheduled for the first week should be conducted within two days before or after the scheduled date. Interviews for the 4th, 8th, and 12th weeks should be conducted within a week, for the 6th month within 2 weeks, and thereafter within 1 month before or after the scheduled date.

Case management will include the following activities:

1) Periodic interviews (either face-to-face or via telephone) with participants

2) Collection of information about each participant's background and treatment status

3) Encouragement of psychiatric treatment to the participants

4) Coordination of appointments with psychiatrists and primary care physicians

5) Encouragement of psychiatric treatment to the participants who have stopped receiving the treatment

6) Referrals to social resources and private support organizations and coordination for utilization of these resources

7) Providing information to participants and the *Psychoeducation Program II* to their family members during hospitalization

8) Providing Internet-based information (website only for the experimental intervention group)

Case managers will conduct periodic case conferences with psychiatrists. The study group management office and the intervention program committee will periodically hold case conference meetings with the study group, visit the participating hospitals, and meet with case managers, as necessary.

Regarding Internet-based information, participants in the experimental intervention group who access the website will receive information about the psychoeducation program, support organizations, and a self-diagnosis program. The dedicated intervention website will contain pages providing an introduction to social resources and serial articles, applied intervention (including psychoeducation and self-evaluation tools), and crisis intervention. The Intervention Program Committee will periodically update the content and articles on the website.

Standard treatment will be provided to subjects in the experimental group at each participating hospital. In addition, each participant in the experimental group will receive a pamphlet on suicide prevention following the psychoeducation program and at hospital visits after enrollment.

Control intervention

Participants in the control group will receive standard treatment with casework at the participating hospitals. Also, participants in the control group will receive a pamphlet on suicide prevention following the psychoeducation program and during their visits for periodic evaluations 6 months after enrollment and every year thereafter.

Evaluations

Psychiatric Evaluations

Evaluators including psychiatrists, clinical psychologists, psychiatric social workers, and/or other mental health professionals, will conduct the psychiatric evaluations. In order to conduct blinded evaluations, evaluators will not know the participants' assigned groups, status of implementation of the intervention, or information on events obtained by other on-site research staff. Moreover, to achieve blinded evaluations, evaluators will not serve as case managers or practitioners in charge of the *Psychoeducation Program II*.

These evaluators will conduct psychiatric evaluations of all participants enrolled at the hospitals and will use a case sheet at 6 months from the date written consent was obtained and every year thereafter until the completion of the study. Evaluations can be carried out up to 1 month before or after the scheduled date.

Evaluations generally will take place as face-to-face interviews at the participating hospitals. The evaluators will notify the participants of the interview schedules 7 days before the scheduled dates via e-mail or regular mail. E-mail messages will be prepared with the e-mail form on the input system and sent via the dedicated e-mail address for this study; the dedicated email address does not permit any replies. Regular mail will be sent by the participating hospitals, and words such as suicide will not be printed on the envelopes. The evaluators will schedule the next evaluation date and inform participants at the end of each interview.

Evaluations will include the following:

1) Participant survival (or cause of death noted in the case of death of the participant)

2) Whether or not suicidal behavior has been repeated

3) Any events other than (1) or (2)

4) Stress factors

5) Persons and/or organizations to consult

6) Treatment status (outpatient or inpatient)

7) Physical function

8) Drinking habits

9) Evaluations using scales

a) Beck Hopelessness Scale [21]

b) Beck Depression Inventory-II (BDI-II) [22]

c) SF-36 [23]

Events

Events will be classified as follows:

1) Recurrent suicidal behavior

2) Total deaths (from any cause)

3) Self-harm

4) Adverse events other than (1), (2), or (3): Any unfavorable and unintended occurrence in a participant, whether or not there is a causal relationship with the intervention, will be recorded.

When identifying an event, the on-site research staff at the participating hospital will record the information according to the event review sheet and will confirm the information with the investigator. If there are no complications, the on-site research staff will enter the content of the event into the web input system. If necessary, on-site research staff will consult with the on-site research coordinator and the study group management office regarding any aspects of the event that are unclear. The on-site research coordinator will notify the hospital director about any serious adverse event and will fax the event review sheet directly to the study group management office.

The data center will consolidate the input data and periodically provide data to the study group management office and the chairperson of the event review committee, according to data management procedures. The study group management office and the chairperson of the event review committee should hold monthly event review meetings to evaluate and assess details of events based on the material provided.

Specific aspects of events will be described in the event definitions and event review procedures.

Time periods during the study

Study period: August 2005 through March 2011

Enrollment period: July 2006 through December 2009

Follow-up period: July 2006 through June 2011

Preconditions for hospital participation in the study

A hospital satisfying the following preconditions may participate in the study: The hospital should have both emergency medicine and psychiatry departments and an established collaborative agreement between those departments, so that the hospital can provide patients with psychiatric interventions to the emergency department.

Within the enrollment period, the hospital can recruit and obtain consent from at least 20 patients who are eligible to participate in the context of inclusion and exclusion criteria. The hospital will perform follow-up on the patients until study completion.

All participating researchers should take a seminar on suicide prevention (epidemiology, risk factors, psychology, prevention, intervention, and postvention). According to their respective roles, each participating researcher may take other seminars on psychiatric diagnosis (Mini International Neuropsychiatric Interview [M.I.N.I.; [24]]), the psychoeducation program, psychiatric evaluation, and assessment by scales (Suicide Intent Scale [18], Beck Hopelessness Scale [21], BDI-II [22], and SF-36 [23]).

Approval of the study protocol

The study protocol will be reviewed and approved by the Central Research Ethics Committee. In principle, the study protocol also will have to be reviewed and approved by the On-site Research Ethics Committee at each participating hospital.

Data collection

Data collection listed will be conducted according to the appropriate timing and each aspect of the relevant information.

Data collected at time of enrollment

1) Basic information on the participant

Initials, ID number, age, gender, other people living with the participant, marital status, education, employment, and other information

2) Information about suicidal behavior

Date and time, means, motivation, Beck Suicide Ideation Scale, and other details of past suicidal behavior

3) Demographic status (items marked with an asterisk on the forms are allocation adjustment factors): Age, gender, history of suicide attempts, DSM-IV diagnosis with M.I.N.I. [24], history of psychiatric treatment, history of