② せん妄の見落としに注意

入院患者の不眠への対応を考えるうえで最も問題となるのは，せん妄の見落としによる不適切な睡眠薬の使用です．

不眠とせん妄は身体治療の場面では表と裏のように常について回ります．どちらも患者のQOLを著しく落とすために確実な対応が必要です．

せん妄は，脳の器質的な脆弱性のうえに，脱水や感染，薬物などの身体負荷が加わったために，脳活動が破綻した状態です．

せん妄の診断基準

A）注意を集中し，維持し，転動する能力の低下を伴う意識の障害
B）認知の変化（記憶欠損，失見当識，言語の障害など），またはすでに先行し，確定され，または進行中の認知症ではうまく説明されない知覚障害の出現
C）その障害は短期間のうちに出現し（通常数時間から数日），1日のうちで変動する傾向がある

〈米国精神医学会診断基準　DSM-Ⅳ-TRより〉

せん妄が生じると，点滴抜去や転倒・転落など医療安全上の問題がよく取り上げられますが，一番の問題は，患者とコミュニケーションがとれなくなることです．その結果，

①患者の意向に沿った治療ができなくなる
②患者の自覚症状が得られなくなり，病状変化の早期発見・早期対応が困難になり転帰が悪化する

ということが生じます．

せん妄というと，一般には術後せん妄を思い浮かべるかもしれません．たしかに術後患者の50％にせん妄が出現します．しかし，一般病棟においても入院患者の約30％にせん妄が合併しています．そのうちの60％が見落とされていると言われています．せん妄がどうして見落とされるのかというと，せん妄の中核症状である睡眠覚醒リズムの障害（いわゆる昼夜逆転）と注意力障害が見落とされるからです．

せん妄のイメージとして幻視や妄想，興奮といった目に見える症状はわかりやすいし，「おかしい」と気付きやすいかもしれませんが，そのような目につく症状の出現頻度はいずれも50％程度しかありません（表2）[3]．その結果，昼夜の区別なく注意力の低下した低活動性せん妄が見落とされてしまいます（あなたの病棟にも，昼もカーテンを引いて寝ているお年寄りはいないだろうか？）．

表2 せん妄の症候と出現頻度

精神神経症状	%	認知症状	%
睡眠覚醒リズムの障害	97	見当識障害	76
幻視・知覚障害	50	注意力障害	97
妄想	31	記憶障害（短期）	88
気分の障害	53	記憶障害（長期）	89
言語障害	57	空間認知障害	87
思考障害	54		
焦燥	62		
制止	62		

文献4より

確実にせん妄を見つけ対応するためには，せん妄の中核症状である睡眠覚醒リズムの障害と注意力障害に注意をしなければなりません（表3）[3]．

ここで1つ症例を紹介しよう．

症例① 66歳　男性

肺腺がんに対する化学療法中の方が発熱と食欲不振のために入院となった．入院してから，「外が暗くなってくると怖くなる」という．受け持ち看護師からも「日中はよく休んでいるけれども，夜になると不安になるようでそわそわとしている．眠れないようだから，何か睡眠薬でも出してもらえないだろうか」と相談があったので，とりあえずゾルピデム（マイスリー®）10 mg/日を出して様子をみることにした．
その晩，病棟から「患者さんが落ち着かない．立ち上がっては転倒し，点滴を抜いて興奮しているので何とかしてほしい」とコールが入った．

この症例では，「日中はよく寝ていて，夜になってそわそわとしている」という点で睡眠覚醒リズムが乱れていること，そわそわと落ち着きがない

表3 不眠とせん妄の比較

	不眠	せん妄
睡眠覚醒リズムの障害	なし	昼夜逆転
症状の動揺	なし	あり (一日のなかでも症状のひどいとき，軽いときがある．一般に夜になると増悪する)
注意力障害	なし	あり (臨床では会話に突然脈絡のない話題が入る．会話が迂遠になりまとまりが悪くなることで気付かれる)
見当識障害	なし	あり (日付や場所，時間がわからなくなる)
記憶障害	なし	あり (数分前のことを覚えていない)
知覚障害	なし	幻視・錯覚
感情の障害	なし	抑うつ状態や躁状態を呈することがある
意欲・行動の障害	なし	あり (亢進して激しく動いたり，逆に発動性が低下することがある)

点で外界の状況を把握できないでいる注意力障害を疑う必要がありました．この時点でせん妄を疑い対応を開始する必要があったのですが，せん妄を見落とし，「不安がっている」との心理的な解釈をして不眠症と誤診をしました．さらに，せん妄のリスクになる超短時間作用型睡眠薬を指示し，結果としてせん妄を増悪させてしまった，ということになります．

③ 不眠とせん妄を鑑別する目をもとう

不眠とせん妄を見極めるためには

- 昼夜逆転がないかを確認する
- 注意力障害の有無を必ず確認する
  ※簡単にできる方法：患者さんと会話をする．話題が脈絡なく飛ぶ場合や直前の話題を忘れていることがあれば，注意力障害を積極的に疑い，せん妄のスクリーニング（見当識の確認，シリアル7※による注意力の確認など）を行う

という，基本を押さえることが何よりも重要です．

参考文献

1）奥山 徹：不眠．『緩和ケアチームのための精神腫瘍学入門』（小川朝生/監，内富庸介/編），p100-115，医薬ジャーナル社，2009 ⇒身体疾患治療中の不眠に関連したアセスメントのしかたについてまとめてある．
2）Ewing JA：Detecting alcoholism. The CAGE questionnaire. JAMA, 252：1905-1907, 1984
3）小川朝生：せん妄．『緩和ケアチームのための精神腫瘍学入門』（小川朝生/監，内富庸介/編），p120-139，医薬ジャーナル社，2009
4）Meagher DJ, et al：Phenomenology of delirium. Assessment of 100 adult cases using stadardised measures. Br J Psychiatry, 190：135-141, 2007

〈小川朝生〉

※100から7を連続的に引いて答えてもらう検査．注意が維持できるかどうかを判断するのに有用

1 せん妄を発症する疑いがある場合

症例

70代 男性

肝がんの局所再発に対して，ラジオ波焼灼療法目的で入院した．自宅では身の回りのこと，金銭管理，買い物も自分でこなしているが，外来受診日をときどき間違えて別の日に受診をしたり，診察券を忘れることがあった．外来で説明したことを忘れて内服を間違えることもあった．前回，ラジオ波焼灼療法目的で入院をした際には，術後にせん妄となり，夜間に興奮したエピソードがあった．

治療内容の説明に訪床したところ，患者から「このところ寝付きがよくない．入院して枕が変わると全然眠れなくなるので，眠り薬を出してほしい」と依頼があった．

1 対応のポイント

高齢者の入院が増えるにつれて，不眠への対応を求められる機会も増えてきたのではないでしょうか．「眠れない」ので睡眠薬を処方したらせん妄になってしまった．このような薬剤が関係した医原性のせん妄の発症頻度は高く，施設内のせん妄の3割程度を占めると想定されています．特にベンゾジアゼピン系抗不安薬と睡眠薬はリスク因子としてあがる代表的な薬剤です．

臨床において一番迷うのが，認知症の診断まではいかない軽い認知機能障害が疑われるような場合，せん妄のリスクをどのように評価し，どのように対応をするか，という判断です．

この症例のように対応に迷う場合，まず考えるのはせん妄発症のリスク評価です．入院・入所においてせん妄を発症するリスクとしてあげられる

項目には，

①高齢（70歳以上）
②認知症
③脳器質疾患の既往（神経変性疾患，脳梗塞）
④運動機能障害
⑤多剤併用
⑥過去のせん妄の既往

など数多く指摘されています．そのうち，最も入院後のせん妄を予測する因子として強いのは，「過去のせん妄の既往」です．

その視点をもって，今回の症例をみますと，前回の焼灼療法時にせん妄を発症しています．さらに，70代であり，認知症の診断はついてはいないものの，「診察券を忘れる」「受診日を忘れる」など軽度の認知障害あるいは初期の認知症を疑うエピソードが既にとられています．今回も同様に焼灼療法後にせん妄を発症するリスクは高いとみなせます．

せん妄のリスクが高い場合，効果的な予防方法はまだ確立してはいませんが，いくつかの研究から，抗精神病薬の予防的な投薬により重症化を防げる可能性は示唆されています．臨床判断としては，患者への説明の後，睡眠薬の処方は避けて，鎮静催眠作用も期待できる非定型抗精神病薬を選択します．

処方例
クエチアピン（セロクエル®）25 mg錠 1回0.5～1錠 1日1回 就寝前

御法度

「不眠だからとりあえず睡眠薬」，「不眠は約束処方で」のような安易な対応は御法度！

参考文献

1）『Delirium：Acute confusional state in palliative medicine』（Augusto Caraceni & Luigi Grassi, ed），Oxford University Press, 2011
2）『これだけは知っておきたい内科医における心のケア』（内富庸介，小川朝生／編），南江堂，2010

〈小川朝生〉

2 せん妄になってしまった場合

症例

70代　男性

膵腺がんに対して化学療法を施行するために入院中．化学療法施行後より，食欲不振が持続，倦怠感も続き臥床がちであった．化学療法施行後7日目から発熱があり，夕方からそわそわと落ち着きのない様子であった．入院時指示の不安時デパス® 0.5 mg 1錠を服用させたところ，「ベッドの下が海になっている」と言い，夜間を通して興奮し続けた．翌日の日中は傾眠がちで過ごしている．今晩の対応について，病棟から主治医に相談がきた．

① 対応のポイント

臨床において，せん妄を発症する典型的なパターンです．せん妄の前駆症状を見落としたために初期対応を誤り，せん妄の発症に至りました．一度せん妄を発症してしまうと，認知機能の回復を図るための治療を行う必要が生じます．

せん妄を発症した場合には，まず

①せん妄の原因を探索する

②原因となる要因のうち，介入・補正が可能な要因は補正を図る

ことを進めますが，入院中の場合にはほとんどの場合に

③症状に対して抗精神病薬による治療を行う

こともあわせて行います．

この症例をみますと，70代とせん妄のリスク（5章-1参照）をもつ患者が，入院をして食欲不振・脱水を生じたところに，発熱と薬剤が重なり，せん妄を発症したと考えられました．

原因としては，1感染，2脱水，3薬剤（チアノジアゼピン系薬剤であるデパス®）があげられ，感染に対してはフォーカスと原因菌を検索した後に抗菌薬の投与，②脱水に対しては経口の補液を進め，③関連する薬剤を中止（この場合はデパス®）にしました．あわせて，せん妄に対して抗精神病薬を開始し，少量から漸増し，必要量を見極めることになります．

同時に重要なのが家族への説明です．家族は今まで普通に会話ができていた患者ができなくなったことに動揺すると共に，どのように接していいのかわからず戸惑います．家族の動揺に配慮をしつつ，原因と治療を中心に今後の見通しを含めて説明します．

家族への説明のポイント

- 家族にせん妄とその原因，治療について説明し，家族の不安を解く（特に精神病や認知症になったのではないことを説明する）．
- 家族の苦労をねぎらう．休養を勧める．
- 家族が介護を抱え込みすぎていないか，疲弊していないか確認する．
- 家族の積極的なかかわりを促す．かかわり方に関する不安を解く（側に親しい人がいるだけでも患者が安心すること，幻視や妄想に無理にあわせなくてよいこと）．

② 家族への説明例（せん妄の説明）

- 今のように，つじつまの合わないような話をされたり，見えてもいないようなものが見えているような状態をせん妄と言います．これは熱が出たり，体の水分が足りないといった体の状態をきっかけに，脳機能がうまく働かなくなった状態です．ぼーっとしてうつらうつらしたり，夜になると混乱して落ち着かなくなったりします．夢と現実が混ぎったような夢うつつのような状態です．
- これは体の症状の1つであり，呆けてしまったとか精神病になったわけではありません．「こころの持ち方」とか「気が弱い」から出てしまう症状でもありません．あくまでも体の病気からきているものです．
- 治療のために入院されている方の場合，2～3割くらいの方が，この症状で困ったり，悩んだりされます．決してまれなことではありません．

せん妄のきっかけになった物事にだけ注目して治療するのは御法度！

薬でせん妄になったら薬だけ中止すればよい，のではなく，必ずせん妄の原因を全身くまなく検索することが必要です．

〈小川朝生〉

自殺未遂者ケア研修テキスト(簡易版)

日本臨床救急医学会
平成25年11月

このテキストについて

～作成の経緯と使い方、注意点など～

日本臨床救急医学会『自殺企図者のケアに関する検討委員会』委員長　三宅　康史

3万人を切ることのなかった自殺による死亡者が、ここ数年ようやく減少傾向が見えてきました。まさに、地道に努力してきた結果であることは間違いありません。

日本臨床救急医学会『自殺企図者のケアに関する検討委員会』も2007年の設置以来、厚生労働省科学研究補助金の支援を得つつ、『自殺未遂患者への対応―救急外来（ER）・救急科・救命救急センターのスタッフのための手引き』（2009年3月）、そして『来院した自殺未遂患者へのケアQ&A―実践編2011』（2011年8月）を刊行するとともに、2008年より厚生労働省が主催する自殺予防に係る行政関係者、医療関係者向けの『自殺未遂者ケア研修』を2009年より共催し、自殺企図者の初療や対応に苦慮する救急医療スタッフ向けに、この『手引き』と『Q&A』をテキストとして使いながら、安全で標準的な初期診療を施せるようサポートしてきました（両冊子ともに、日本臨床救急医学会ホームページのトップページ〔お知らせ〕⇒右下にある過去のお知らせをクリック⇒2011/9/12のところでPDFが無料でダウンロードできます http://jsem.umin.ac.jp/history.html）。

しかし、この研修は受講料無料で毎年開催されるとはいえ、例年、全国3か所（1か所につき最大50人程度）で約150人程度しか受講できず、全国の自殺未遂者ケアへの関心の高い地方自治体を中心に、もっと多くの開催を希望する声がありました。そこで、当委員会として、厚生労働省主催の1日研修を約4時間の半日に凝縮して、講義はこのテキストで自己学習していただき、典型的な症例について専門スタッフ（精神科医、精神保健福祉士、臨床心理士）をファシリテーターとして、患者さんやその家族の直面する問題点を丁寧に洗い出し、医療面や行政面など多方面から実現可能な解決法を探るスモール・グループ・ディスカッションを中心とした学会版（簡易版）研修を企画しました。参加対象は、現場の医師、看護師を中心とした医療スタッフ、保健師、行政官、教員などです。次のページに平成25年度版厚生労働省主催『自殺未遂者ケア研修』の案内パンフレットの1ページ目を掲載しておきます。ご参照のうえ、この学会版との違いなどご確認下さい。

この冊子は学会版（簡易版）のためのテキストです。厚生労働省主催の自殺未遂者ケア研修で中心的な役割を果たしてきた講師陣による講義内容のパワーポイントをそのままハンドアウトとしたものです。学会と地方自治体による研修会ですので、中で使用される写真や図には版権の存するものがあるやもしれませんが、基本的に非売品（製本、発送など諸費用は別）で、学習のための私的な教材との位置づけです。もちろん今回の作成にあたっても厚生労働省科学研究補助金の支援を受けております。

以上、このテキストの作成の経緯、使用上の注意点などに十分配慮の上、このテキストで今まで不安に考えていた自殺未遂者ケアを、科学的かつ合理的に理解し、今後の自信の源としていただければ、作成者としてその目的はほぼ達成されたといえます。

なお、学会版（簡易版）自殺未遂者ケア研修の開催を希望される方は、日本臨床救急医学会事務所 jsem-gakkai@umin.ac.jp までお問い合わせください。

厚生労働省主催

「自殺未遂者ケア研修（一般救急版）」

自殺未遂者への対応にお困りになられたことはありませんか？
本研修は、初期対応から継続的な支援まで、臨床現場で役立つ自殺未遂者ケアのポイントを、日本臨床救急医学会が厚生労働省と共に作成したガイドラインに沿って体系的に学んでいただくと共に、モデル症例によるワークショップを通じケアのあり方を実践的に修得していただく内容です。
講師とファシリテータは、自殺未遂者のケアを実践している専門家・専門職が務めます。
奮ってご参加のほどお願い申し上げます。

●主　催：厚生労働省
●共　催：一般社団法人　日本臨床救急医学会
●参加費：無料（定員50名）
●対象者：救急医療に従事する医師、看護師、その他コメディカルスタッフなど
●会場・開催日：
【東京会場】平成26年1月25日（土）9：50～16：45
東京ファッションタウン（TFT）ビル東館　9階909研修室
〒135-8071　東京都江東区有明3-6-11
【岡山会場】平成26年2月22日（土）9：50～16：45
第一セントラルビル1号館　9階大ホール
〒700-0901　岡山市北区本町6-36
【仙台会場】平成26年3月9日（日）9：50～16：45
フォレスト仙台　2階第7会議室
〒981-0933　仙台市青葉区柏木1-2-45

●お申込み
【お申込み締切日　東京会場：1月4日、岡山会場：1月24日、仙台会場：2月10日】

メールでのお申込み　下記アドレスに裏面の申込書記載事項とともに、お申込みください。
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FAXでのお申込み　裏面の申込書に必要事項をご記入の上、お申込みください。
FAX：03−6454−2482「自殺未遂者ケア研修参加受付係」

●プログラム

9:30	開場	
9:50～10:00	事前アンケート	
10:00～10:10	開会挨拶	
10:10～10:30	講義1	「自殺未遂者対策がなぜ必要か」
10:30～10:50	講義2	「自殺未遂者ケア・モデルと地域自殺対策」
10:50～11:05	講義3	「国と地方自治体の自殺対策の取組み」
11:05～11:35	「自殺未遂者ケアガイドラインとワークショップの説明」	
11:35～12:35	昼休み	
12:35～16:05	ワークショップ、成果物発表とディスカッション（途中休憩2回あり）	
16:05～16:25	講義4	「自死遺族への対応と支援」
16:25～16:35	事後アンケート	
16:35～16:45	閉会挨拶	

※ワークショップはモデル症例について救急医療施設における自殺未遂者への対応をグループで討議します。
都合によりプログラム内容が一部変更になる場合がありますので、予めご了承ください。

●お問合せ
自殺未遂者ケア研修参加受付係
自殺未遂者ケア研修事務局　㈱フォーラムワン内
電話：03−6454−2478　FAX：03−6454−2482
対応時間：午前9時～午後6時（土日・祝日を除く平成25年3月

「自殺未遂患者への対応:救急外来（ER）・救急科・救命救急センターのスタッフのための手引き」作成班

有限責任中間法人　日本臨床救急医学会
「自殺企図者のケアに関する検討委員会」
担当理事
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山田　朋樹（横浜市立大学）
協力
伊藤　弘人（国立精神・神経センター）
河西　千秋（横浜市立大学）

「来院した自殺未遂者へのケア Q&A ―実践編2011―」 執筆
大塚耕太郎（岩手医科大学）
河西　千秋（横浜市立大学）
岸　泰宏（日本医科大学）
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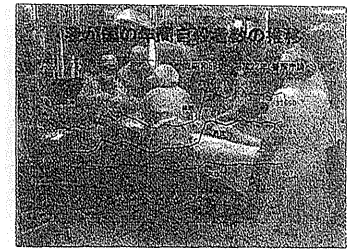
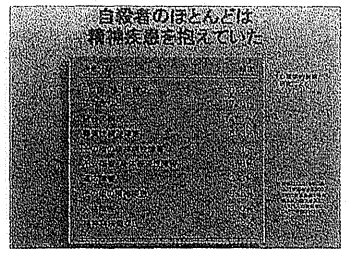
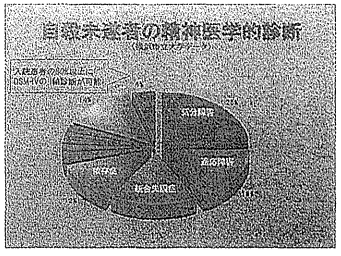
目　次

本テキストは、平成25年度厚生労働科学研究費補助金（自殺未遂者および自殺遺族等へのケアに関する研究）の支援を受けて日本臨床救急医学会が作成した。

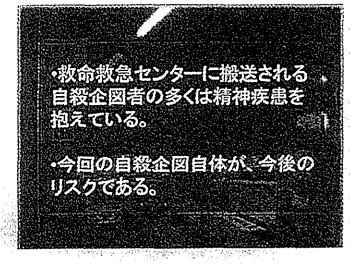


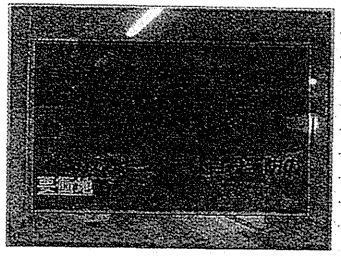


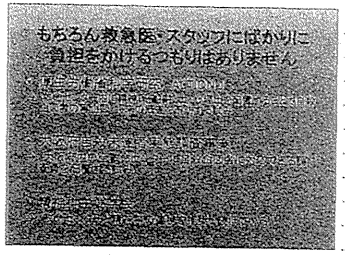

自殺未遂者の精神医学的診断

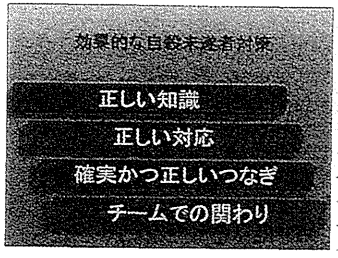

自殺の三大危険因子
精神疾患


自殺企図の既往は、
自殺の重大な危険因子


•救命救急センターに搬送される自殺企図者の多くは精神疾患を抱えている。
•今回の自殺企図自体が、今後のリスクである。

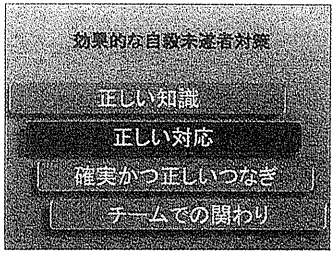

緊張感

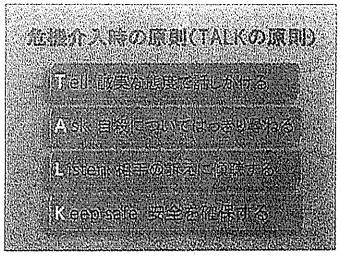

もちろん救急医、スタッフにばかりに負担をかけるつもりはありません

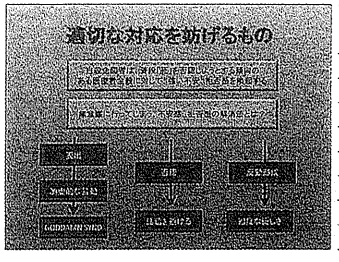

効果的な自殺未遂者対策
正しい知識
正しい対応
確実かつ正しいつなぎ
チームでの関わり


効果的な自殺未遂者対策
正しい知識
正しい対応
確実かつ正しいつなぎ
チームでの関わり


自殺企図者の心理状態を理解する
「視野狭窄」
「両価性」
「衝動的行為発現」


効果的な自殺未遂者対策
正しい知識
正しい対応
確実かつ正しいつなぎ
チームでの関わり


危機介入時の原則(TALKの原則)
Tell 勇気を持って話しかける
Ask 自殺について率直に尋ねる
Listen 相手の気持ちに傾聴する
Keep safe 安全を確保する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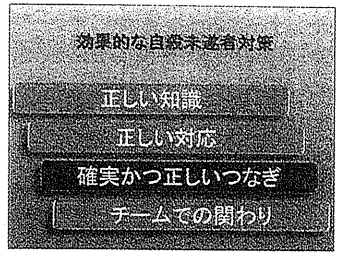
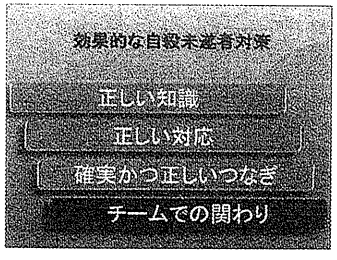

効果的な自殺未遂者対策
正しい知識
正しい対応
確実かつ正しいつなぎ
チームでの関わり


<身体治療終了≠退院>


効果的な自殺未遂者対策
正しい知識
正しい対応
確実かつ正しいつなぎ
チームでの関わり


福祉
医療
みんなでつながり、みんなで支える

Mental Health Care Reforms in Asia

The Regional Health Care Strategic Plan: The Growing Impact of Mental Disorders in Japan

Hiroto Ito, Ph.D.
Richard G. Frank, Ph.D.
Yukiko Nakatani, M.D., Ph.D.
Yusuke Fukuda, M.D., Ph.D.

In April 2013 Japan designated mental disorders as the fifth "priority disease" for national medical services, after cancer, stroke, acute myocardial infarction, and diabetes. All prefectures will be required to assess local mental health needs and develop necessary service components. This column provides an overview of the Regional Health Care Strategic Plan in the context of mental health and welfare reforms. The goals of the plan are to alter the balance between institutional and community-based care for patients with severe and persistent mental disorders, integrate general medical and mental health care, and support greater independence for people with mental disorders. It is a political challenge for Japan to reallocate resources to rebalance care services while maintaining free access to care. (*Psychiatric Services* 64:617–619, 2013; doi: 10.1176/appi.ps.201200518)

Dr. Ito is affiliated with the Department of Social Psychiatry, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-Higashi, Kodaira, Tokyo 1878553, Japan (e-mail: itohiroto@ncnp.go.jp). Dr. Frank is with the Department of Health Care Policy, Harvard Medical School, Boston. Dr. Nakatani is with the Essential Medicines and Health Products Department, World Health Organization, Geneva. Dr. Fukuda is with the Japan International Cooperation Agency, Tokyo. Howard H. Goldman, M.D., Ph.D., served as editor of this column.

Introduction by the editor: In this issue of *Psychiatric Services,* we are pleased to launch a new column, Mental Health Care Reforms in Asia, which joins columns on mental health reforms in Europe and in Latin America. Reforms are emerging in Asia as well, and the journal plans to stay abreast of developments and report them to our readers. In this column, Dr. Ito and his colleagues describe a new mental health planning process in Japan. In April 2013 mental disorders were identified as a priority disease for attention of policy and program development in Japan. This is an unprecedented opportunity to reform the mental health service system and mental health policies in the rapidly aging island nation with a surfeit of hospital beds and a limited outpatient sector.

In Japan, a key challenge is to rebalance the provision of mental health care from institutions to the community. This column provides an overview of a new strategic plan in Japan to guide policy and address challenges in reallocating mental health resources while maintaining free access to medical services. Japan's universal health insurance system has successfully promoted good health at a reasonable cost for the Japanese population (1,2). However, in the 50 years since universal coverage was instituted in 1961, new challenges have emerged. In Japan, physicians can open clinics and practice in any location they choose, and there are no limits on utilization of inpatient care. Although this arrangement allows for a great deal of freedom, it also means that no organization or profession has responsibility for the care of a defined population. There are thus few incentives to consider all the needs of patients and to view care from a longitudinal perspective. At the same time, health care spending is rising in Japan as the mean age of the population increases. Currently, persons over age 65 account for 23% of the Japanese population (3), compared with about 13% of the U.S. population. These trends have driven an important political impulse to reallocate resources to attenuate the impacts of both rising health care spending and the aging population.

Mental disorders have a growing impact on the health of the Japanese people and impose an increasing burden on the health care delivery and financing systems. The number of patients with mental disorders who are treated by physicians now exceeds the number of patients with diabetes (4). In most Asian countries, inpatient care has been the treatment of choice for people with mental disorders (5), in contrast to many nations in the Organization for Economic Cooperation and Development. In Japan, there are 2.7 psychiatric beds per 1,000 persons, with private nonprofit organizations accounting for 91% of these beds (6). In 2010 the average length of a psychiatric inpatient stay was 301 days (6); 18% of psychiatric beds were occupied by patients who stayed less than three months, 15% by patients who stayed from three months to one year, and 67% by those who stayed for more than one year (7). Spending for psychiatric inpatient care was estimated at 1,459 billion yen (US$16 billion), which represents 10.4% of all spending on inpatient care for all conditions (US $1=JPN¥90) (8). A shift from hospital- to community-based care is increasingly necessary in Japan.

In April 2013, mental disorders were designated as a priority disease for national medical services in Japan, the fifth priority after cancer, stroke, acute myocardial infarction, and diabetes. The Japanese government announced a new national initiative, the Regional Health Care Strategic Plan. Beginning in 2013, all prefectures in Japan will, for the first time, be required to assess local mental health care needs and develop necessary service components. The plan requires local governments to determine the availability of mental health services and identify actions to address local needs, allocate resources, and evaluate the progress.

The Basic Policy for Mental Health and Welfare Reforms

The government released the national guidelines for the Regional Health Care Strategic Plan to all prefectures in March 2012. The national guidelines build on the Basic Policy for Mental Health and Welfare Reforms of 2004 (the Basic Policy) (9), which established a mechanism to encourage a shift from hospital to community care. The Basic Policy was revised in 2009 (10), with four new principles designed to significantly reduce the number of inpatients and prevent new episodes of long stays in psychiatric hospitals. First, mental health care should be differentiated according to the focus of provider efforts on emergency, acute, or chronic care. More personnel and economic incentives should be given to providers of emergency and acute care. The Basic Policy requires that acute care providers must increase the intensity of their services and their expansion of community-based services. Second, government should assist providers in improving the quality of mental health care. Third, social support services should be expanded in the community. Fourth, public education about mental illness and treatment is needed, and the voice of service users should play a stronger role in policy making.

The Regional Health Care Strategic Plan

Individual prefectures will be expected to create plans for mental health services and to implement and evaluate services according to the national guidelines. This represents a rare opportunity for each prefecture to incorporate into health service planning its priorities for serving its population. This change is significant because regional control of services in Japan is not the usual arrangement. The goals of the Regional Health Care Strategic Plan are to alter the balance between institutional and community-based care for patients with severe and persistent mental disorders (for example, schizophrenia); integrate care for general medical and mental health conditions (for example, depression); and support greater independence for people with mental disorders, including older adults with behavioral and psychological health problems (for example, dementia). Each prefecture will set up a committee to develop a plan and monitor progress. The level of authority given to these committees is an issue that will be decided as implementation evolves.

Each plan must specify community action plans that target specific conditions, mainly schizophrenia, depression, and dementia. Several principles of the Regional Health Care Strategic Plan must be addressed. The Basic Policy must lead to a comprehensive community-based system. The system should provide access to general medical and nursing care as well as social services and employment support services. Hospitals must ensure appropriate staffing and emphasize discharge support through collaboration with other community service providers. Patients and their families should be informed of services available in the community.

Each prefecture must assess its needs and develop a strategic plan for prevention, access to services, treatment, recovery, rehabilitation (inpatient and outpatient), emergency psychiatric care, and complications resulting from general medical illnesses. Each prefecture will use quantified performance targets for the development and implementation of strategic plans, including the suicide rate, length of hospital stay, rate of readmission within three months, and rates of health center consultation, day treatment use, nursing service visits, and emergency care.

Vertical coordination

The Regional Health Care Strategic Plan is expected to promote better coordination between inpatient and community care for people with mental disorders. Local programs are developing evidence-based approaches to community-based treatment programs for people with mental disorders. Alternatives to hospital care include evidence-based outreach services, such as assertive community treatment (ACT) programs, early intervention programs, and day treatment services. ACT has been shown to be a cost-effective alternative to long-term inpatient care (11), and some ACT programs have begun to take root in Japan (5). ACT focuses primarily on people with severe and persistent mental illness. Currently, ACT services are available in limited areas in Japan; some psychiatric clinics provide outreach services with psychiatrists, nurses, and psychiatric social workers. ACT programs will be expanded beyond the few areas where they have been launched, with the aim of preventing hospital readmission. Day programs have been reimbursed in Japan since 1974. The total per-day reimbursement for participation in a day program and outpatient care is equivalent to the cost per day of long-stay inpatient care. This reimbursement scheme has helped newly admitted psychiatric patients use community services after hospital discharge. Housing for people with mental disorders, including group homes, is gradually increasing, despite the limited national budget for such programs. These community services must be backed up by acute inpatient services.

One new effort seeks to expand the use of patient-initiated discharge plans

that include crisis resolution. On discharge to the community, the patient and multidisciplinary staff jointly develop an individualized plan. It includes a crisis plan that addresses how the patient should respond to the crisis and seek help when his or her condition is not stable. Because the patient's needs and preference are reflected in the plan, better compliance is expected.

Horizontal integration

Early recognition and diagnosis of mental disorders increases the likelihood of successful treatment, which highlights the need for education, training, and support for primary care physicians. The goal is to create a system that facilitates patients' entry into specialized care—a system in which community health services and family physicians refer patients with significant mental health needs to psychiatrists and specialty mental health providers connect patients with other types of medical needs to general medical services and those with human service needs to social services.

Under a 2012 initiative of the National Center of Neurology and Psychiatry in Japan, national specialized care and research centers (cancer, cardiovascular disease, global health and medicine, child care, geriatric care, and neurology and psychiatry) launched collaborative care programs focused on depression diagnosis and treatment to integrate mental health care with general medical care. Scientific and practical collaboration with professionals treating general medical illnesses contributes to a better understanding of mental health among health care providers.

Challenges

Implementation of plans for the four other diseases with priority status has encountered several problems. Prefectures were interested in being perceived as successful, which created an incentive to propose the minimum targets allowed. As a result, the plan-do-check-act cycle has not worked well. For mental disorders, the fifth priority disease, indicators are being used to reinforce the plan-do-check-act cycle. However, local governments do not have experience in developing regional mental health plans, and the initiative will tax their technical capacity. Regional differences in the quality and implementation of the action plans are therefore expected. Although some variation is appropriate, the goal is to minimize variation, and each prefecture will need to develop indicators specific to its health care system.

Financial incentives to focus on acute care and to promote community services do not lead directly to fewer psychiatric beds because private psychiatric hospitals have added community programs to conventional institutional care. Each prefecture's plan must address the appropriate number of psychiatric emergency beds and acute care beds; however, the closure or reduction of chronic care units remains open for discussion.

Finally, concerns have been raised about the capacity of the community service systems to respond to the vastly increasing needs of the population requiring mental health care. Sustainable funding of community care systems is always a challenge. Good community care, although cost-effective, requires significant investments. Funds for developing community services can be expected from the savings achieved by reducing inpatient care, but such conversion is often not easily realized. Currently, ACT is reimbursed not as ACT per se but as a combination of home care and visiting physician and nursing services. In some cases, this may result in implementing models that do not adhere to what has been shown to work. To promote these intensive and complex services, a payment system is needed that makes providing these services viable in community-based programs. Payment policy in this area is controversial.

Conclusions

In line with the increasing prioritization of treatment for and prevention of mental disorders in Japan, development and implementation of the Regional Health Care Strategic Plan will be mandatory in the prefectures. The government has made it a priority to shift care from hospitals to communities closer to patients' homes. The balance between institutional and community care is delicate, but it is the key to success. By implementing deinstitutionalization gradually, Japan will have the advantage of continuing to learn from the experiences of other countries.

Acknowledgments and disclosures

The authors report no competing interests.

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REVIEW ARTICLE

What Should We Do to Improve Patients' Adherence?

Hiroto Ito*

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ARTICLE INFO

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KEY WORDS:
adherence;
compliance;
medication management and use;
shared decision-making

Adherence to treatment regimens is lower than what physicians expect. The impact of poor adherence on treatment outcomes and healthcare costs is significant. As the number of prescribed medications increases with the rising prevalence of chronic diseases and multimorbidity, the risk of nonadherence also increases. This article reviews the research that has explored effective interventions to improve patient adherence to treatment. Recent literature, including meta-analyses and systematic reviews on patients' adherence, were examined in the present study. Barriers to adherence exist at the level of the patient, the healthcare provider, and the healthcare system. Patients' adherence is measured by many methods such as self-report, pill counting, and the medication possession ratio. No single standard intervention exists that improves adherence; however, a combination of interventions seems to be more effective than individual interventions. Physicians and pharmacists should simplify regimens in consideration of a patient's health literacy. Patient education should include behavioral support and reminders through a multidisciplinary approach that involves case management and collaborative care. Shared decision-making ensures the alignment of care with a patient's preferences and value so that they are motivated to participate in medical care. Combined interventions are more effective than individual interventions. Patients' active participation in treatment through shared decision-making is important.

1. Introduction

Patients' nonadherence may be a common underlying cause of treatment failure. The premise is simple. No matter how advanced a drug is, if the patient does not take it properly, the patient and the physician cannot expect to receive the full benefits of the medication. Poor adherence often hinders treatment, especially in patients with chronic diseases such as hypertension or diabetes.[1] The prevalence of chronic diseases is rising with the aging population, and the most common chronic condition in adults is multimorbidity.[2] As the number of prescribed medications increases, the risk of nonadherence also increases. These trends highlight the importance of patient adherence.

Adherence has been the focus of extensive research for decades. This paper reviews the research evidence with regard to effective interventions that improve a patient's adherence.

1.1. What is adherence?

In 2001, the World Health Organization defined the term "adherence" as "the extent to which the patient follows medical instructions".[2] The word "adherence" is preferred to "compliance" because "compliance" suggests that patient is a passive follower of the doctor's orders, whereas the word "adherence" implies that the treatment plan is based on a therapeutic alliance between the patient and the physician.[3] Adherence commonly refers to the patient taking the medication as prescribed; however, the scope of adherence covers all recommended health behaviors such as healthy lifestyle habits and clinic appointments.

1.2. Physicians underestimate the true adherence rate

Poor medication adherence is a serious problem because nearly one-half of patients with chronic diseases do not take their medications as prescribed.[3,4] Adherence to treatment regimens is relatively high in clinical trials because of the strict selection process for enrolled patients; however, only 43–78% of patients with chronic diseases maintain good adherence to medication.[4] The adherence rate is likely to decline over time. By using prescription data on statin therapy in elderly patients, Benner et al.[5] found that 21% of patients stop taking their prescribed medicines within 3 months, and 44% of patients stop taking their medication within 6 months. Medication adherence by patients is better than their adherence to other therapeutic regimens. A meta-analysis shows suboptimal adherence rates to medication (79.4%), screening (72.8%), exercise (72.0%), healthy behaviors (69.7%), clinic appointments (65.9%), and diet (59.3%).[6] To adhere to treatment regimens that cause a lifestyle change is more difficult for patients.

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Because patients often pretend to follow the physician's instructions during consultations, adherence to treatment regimens improves for a short time just prior to a clinic visit. This behavioral characteristic is known as the "white-coat effect."[7] A study of patients with epilepsy showed a marked decline in adherence levels in the interval between appointments.[7] The percentage of patients who take medicines as prescribed are 88% for 5 days prior to a clinic visit and 86% for 5 days after the visit; however, this rate declines to 67% 1 month after the visit.[8] Physicians are often disappointed with low treatment adherence; however, treatment adherence around the visit is usually better than during the interval between visits. A previous study reported that more than one-third of patient-reported adherence is not correctly estimated by physicians.[9]

1.3. Low adherence compromises patient outcomes

Nonadherence has negative consequences. Failure to follow prescriptions causes preventable mortality, morbidity, and approximately 10% of hospital admissions,[10,11] and costs billions of dollars each year.[12] Adherence is not limited to medication, therefore the impact of nonadherence is substantial. Patients with diabetes, hypertension, hypercholesterolemia, or congestive heart failure who have high adherence scores have a lower risk of hospitalization than patients with low adherence scores, and patients who have low treatment adherence for diabetes and hypertension have a higher risk of hospitalization.[13] A meta-analysis of 63 studies reveals that low adherence to medication, diet, and exercise is associated with worse overall outcomes (26%) and with intestinal disease (40%), sleep apnea (31%), hypertension (30%), and hypercholesterolemia (25%).[6]

2. Barriers to adherence

There are three levels of barriers to adherence: the patient, the healthcare provider, and the healthcare system.[3,14] These factors are interwined and affect adherence. At the patient level, identified factors include age, socioeconomic status, lifestyle and health beliefs, forgetfulness, and previous treatment failure. In addition, mental health problems such as depression underlie nonadherence. Depressed outpatients are 2.4-fold more likely to forget and 2.2-fold more likely to skip their medications, compared to their nondepressed counterparts.[15] Depressed patients have a 3-fold overall greater risk of nonadherence, compared to nondepressed patients.[16] Patient adherence is also affected by a healthcare provider's practice, including their prescribing of complex treatment regimens, insufficient explanations of drug actions and adverse effects, and lack of communication with patients regarding their lifestyle and economic conditions.[3] A good patient–physician relationship has positive impacts on adherence to treatment.[17]

Adherence is influenced by the healthcare system.[3] Changes in a reimbursement system may affect patient behavior. Patients may not continue costly treatment because of difficulty affording out-of-pocket expenses. If physicians are unaware of such behaviors of their patients, the patients may become less adherent to treatment regimens or may even discontinue treatment. In a systematic review, increased out-of-pocket expenses have been identified as a barrier to adherence at the healthcare system level.[18]

3. Measuring adherence

An accurate measurement of adherence is necessary; however, there is no gold standard. Adherence is measured by various methods. The most appropriate way of measuring adherence depends on the situation since each method has its advantages and disadvantages.

3.1. Patient self-report

The simplest way to check adherence is to ask patients: "Do you take your medication as directed? I know it must be difficult to take all your medications regularly." [3] The key to such direct questioning is to allow patients to answer "Yes" or "No" to a closed-ended question.[19,20] Patients may keep diaries to show their healthcare providers. The problem with these approaches is that patients often overestimate their adherence level, although they may be less susceptible to recall bias.[21]

3.2. Questionnaire

Questionnaires have been developed to improve the accuracy of patient reports. The reliability and validity of these questionnaires have been established. The Medication Adherence Questionnaire (MAQ) is the most commonly used adherence scale.[22] The scale was originally developed for hypertension, and was later expanded for use in other diseases. Unlike the MAQ, the Self-efficacy for Appropriate Medication Use Scale (SEAMS)[23] and the Brief Medication Questionnaire (BMQ)[24] assess self-efficacy in evaluating medication adherence. The Hill-Bone Compliance Scale is used in cardiovascular disease.[25] The Medication Adherence Rating Scale (MARS)[26] is often used in mental disorders.[27]

3.3. Pill count

Prescription or pill-based methods estimates a patient's medication adherence by using the dates of prescription refills or pill counts during routine clinic visits.[28] It is easy to monitor a patient's adherence to medication in clinical settings. These methods are often used in clinical trials; however, prescription refill records and pill counts are not sufficiently objective. Patients may simulate adherence by emptying their pill bottles just prior to a clinic visit,[19] and pill counts often overestimate true adherence rates.[20]

The Medication Event Monitoring System (MEMS) and Doser (Meditrack) have been developed to replace pill counts.[19] These systems electronically record the time when the bottle is opened. There is still a concern that a patient may not have taken a pill, even though the bottle was opened. These electronic monitoring systems are expensive, and may not be feasible for clinical practice.[21]

3.4. Medication possession ratio

Administrative data can be effectively used for measuring adherence. The medication possession ratio (MPR)—defined as the number of days for which prescription medication is supplied divided by the days of observation—is useful because it can be easily calculated from a medical chart and does not require continuous measurement.[29] In contrast to the pill count of a patient's pill bottle, the MPR is calculated by using an administrative database, primarily a computerized pharmacy system.[30] The MPR is used as a quality indicator but it requires a closed pharmacy system.[3]

3.5. Serum drug level monitoring

The most accurate way to assess recent adherence prior to a clinic visit is through measuring the serum or urine levels of a medication or its metabolites.[31] The timing of doses, however, is unknown, and some drugs are not easily monitored at clinic visits.[21] This method

would detect only the "white-coat effect" because the serum drug level only shows a patient's adherence within several days prior to the visit.[31] The method is also expensive[4] and is the least acceptable method to patients.[32]

4. Combined interventions

The effect of interventions on improving adherence varies among studies and there is no single standard intervention.[4,18] But it is known that the more comprehensive the approach is, the more adherence is improved.[33] Therefore, a combination approach is key to improving adherence. Each intervention should take into consideration of the balance between adherence benefits and costs.

4.1. Simplified regimen and health literacy

Unless patients do not understand their disease and treatment, physicians cannot expect high patient adherence. The first thing physicians need to do is to simplify treatment plans,[34,35] and to use simple and clear directions with explicit language to instruct patients. It is particularly important that physicians assess the level of health literacy and understanding of their elderly patients.[36,37]

Limited health literacy impedes patient comprehension of medication instructions.[38] Health literacy is defined as "the degree to which individuals can obtain, process, and understand the basic health information and services they need to make appropriate health decisions."[39] The adherence rate is higher if the patient takes a medication once a day; however, the adherence rate declines as the number of doses increases.[35] Wittlicke et al.[39] found that the most prevalent complex characteristics of a medication regimen are: the prescription of one or more drugs with multiple daily doses; the prescription of three or more drugs with different dosing intervals; and tablet splitting. Another study showed that problems with interpreting medication instructions are most commonly caused by the frequency of hourly intervals (e.g., "take 1 pill by mouth every 12 hours with a meal") or by the number of times of day (e.g., "take two tablets by mouth twice daily"), whereas patients are less likely to misinterpret prescription instructions that use time periods (e.g., "take 2 pills in the morning") or specific times (e.g., "take 1 pill at 8 AM").[38] Simple modifications of the medication scheme can reduce one-fifth of the complexity of a regimen.[40]

Physicians may hesitate to give patients negative information such as the adverse effects of medications. Hynese (2008) posed the following question: "Does telling about adverse effects of medication lower adherence?"[4] Several studies have shown that explaining to patients about the adverse effects of their medications does not affect their use of the medications.[4] Lower adherence may be independent of informing of patients regarding side effects.

4.2. Patient education and behavioral support through a multidisciplinary approach

The provision of educational materials alone does not greatly modify patient behavior. Combined educational interventions such as behavioral support with educational materials for several weeks or months are effective for chronic diseases such as hypertension, hyperlipidemia, heart failure, and myocardial infarction.[18] Reminders are important in assisting healthcare providers improve patient adherence. Daily video-telephone or regular telephone reminders[41] and monthly educational letters to patients emphasizing the importance of adherence to treatment[42] are effective in enhancing patient medication adherence.[43,44] In a systematic review, reminders by manual phone calls are more effective than automated reminders, but there is no strong effect if the time between the reminder and the appointment is within a week.[45] Reminders are also the least costly intervention.[46]

In addition to physician efforts to improve patient adherence, other healthcare providers (e.g., nurses, social workers and pharmacists) also have roles to play in a multidisciplinary team approach. Case and medication management are major components of team care.[18] A multidisciplinary team approach has been proven as effective for improving the adherence of patients with diabetes,[47,48] hypertension,[49] heart failure,[50] or depression.[47–49, 51–53] Collaborative care also effectively improves adherence in patients with comorbid depression and chronic illness.[54] Collaborative care is defined as a multifaceted intervention involving the combination of three distinct professionals working collaboratively within the primary care setting: (1) the case manager, (2) the primary care practitioner, and (3) the mental health specialist.[55,56]

The involvement of a clinical pharmacist in multidisciplinary care through assessing patient knowledge and providing instructions about medication use leads to greater medication adherence.[57,58] Pharmacist-provided medication therapy management and a patient's use of medicine consists of patient education and the discussion of problems, but professional input is effective.[46]

4.3. Shared decision-making

An important concept in the practice of healthcare has shifted to shared decision-making, which implies a paradigm of patient adherence.[59] In current practice, the nature of the patient–physician relationship is quite different from the traditional paternalistic model, which is characterized by the physician exercising great control. In place of such an authoritarian approach, a relationship of mutuality is increasingly common in which physicians treat patients as partners and encourage their patients' active involvement in treatment plans. In shared decision-making, the physician offers options with risks and benefits, whereas the patient expresses his or her preferences and values. Thus, the physician and patient both have a better understanding and share responsibility in the decision-making.[60]

Shared decision-making requires patient education and requires physicians to make an effort to improve communication with patients.[60] Poor communication is independently associated with objectively measured inadequate medication refill adherence.[61] Patient adherence to treatment regimens is 2.16-fold greater with physicians that have high communication skills; physician communication training can improve patient adherence by 1.62-fold.[17] Shared decision-making improves medical care—particularly in patients with chronic diseases—and reduces costs; however, its implementation in clinical practice is slow.[62]

5. Conclusion

There is no gold standard with which to measure and improve patient adherence, although various measurements such as pharmacist-provided interventions have been developed. Combined interventions are more effective than individual interventions. Because shared decision-making is emphasized in the practice of healthcare, healthcare providers including clinical pharmacists must focus on the active involvement of their patients. Physicians and patients should both have a better understanding of information and should share responsibility in the decision-making on medication management and medication use. In this way, optimal patient adherence can be achieved.

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Heart Disease and Depression

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Depression is common in patients with physical illness. The National Center of Neurology and Psychiatry has launched a joint project with five other centers in Japan, aiming at improving the quality of mental care in patients with physical illness. In the present overview focusing on heart disease, we review the prevalence of depression in patients with heart disease, the impact of depression on cardiac prognosis, the possible mechanisms of depression in patients with heart disease, drug-drug interactions between cardiac and psychotropic agents and the possible therapeutic approaches to treating these patients. Depression and heart disease often coexist and each can lead to the other. Various biological and behavioral mechanisms have been proposed to explain an association between heart disease and depression, including autonomic nervous system activity, impairment of platelet function, endothelial dysfunction, inflammatory changes, and health-related behaviors. Combination therapy with tricyclic antidepressant and cardiac agents must be approached with caution to avoid drug-drug interactions. Selective serotonin reuptake inhibitors (SSRIs) are the first line treatment for patients with heart disease and moderate to severe depression. Although no single intervention has been established as the standardized treatment, recent studies suggest that collaborative care improves both depressive symptoms and cardiac outcomes, and that patient's participation is a key to successful treatment. Bridging the gap between cardiology and psychiatry is essential, and psychiatrists can play a vital role in taking care of the mental health of patients with heart disease.

Key words: depression, heart disease, antidepressant, collaborative care
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Introduction

Depression is a subject of growing importance in patients with physical illness. The prevalence of depression varies according to the definition and assessment methods. In general, the prevalence of depression is 13%-20% in patients with cancer [1], 29%-36% with stroke [2], 20% with coronary heart disease [3], and 11% with diabetes mellitus patients [4]. Negative impacts of depression on the outcomes of patients with physical illness are well-known. Depression may raise the mortality risk of patients with cancer 1.25-fold [5] and double the risk in those with myocardial infarction [6], while depression increases the length of stay in hospitalization and clinic visits in patients with stroke [7]. Also, depression may reduce glycemic control [8] and adherence to treatment in patients with diabetes mellitus [9].

To improve the quality of mental health care in patients with physical illness, the National Center of Neurology and Psychiatry (NCNP) has launched a joint project with five other national centers in Japan, including the National Cancer Center (cancer), the National Cerebral and Cardiovascular Center (stroke and heart disease), the National Center for Global Health and Medicine (diabetes mellitus), the National Center for Geriatrics and Gerontology (dementia), and the National Center for Child Health and Development (chronic inflammatory bowel disease). The project is aimed at promoting (A) training of health care providers in medical fields, (B) certification of model institutions and communities to provide high quality of mental health care for patients with physical illness, and (C) clinical research on the effectiveness of collaborative care programs and a support network to facilitates the integration of mental health care into general health care.

In the present overview, we are focusing on heart disease, and we review the prevalence of depression in patients with heart disease, the impact of depression on cardiac outcomes, the possible mechanisms of depression in patients with heart disease, drug-drug interactions between cardiac and psychotropic agents, and the possible therapeutic approaches to treating these patients.

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Prevalence of Depression and its Impact on Cardiac Outcomes

There is a growing body of literature on an association between heart disease and depression. "Heart disease" is a broad term to describe a range of diseases in the heart, including coronary heart disease or coronary artery disease, heart attack, and heart failure. The result of a meta-analysis shows that 20% of patients with coronary heart disease have depression [3]. The results of follow-up community-based study over the past decade show moderate to strong relationships between depression and heart disease such as angina and myocardial infarction [10]. A Swedish twin study in 2009 suggested that heart disease increases the incidence of depression risk 2.8-fold times (95%CI: 1.9-4.2), while depression increases the incidence of cardiovascular disease 2.5-fold times (95%CI: 1.7-3.8) [11]. Patients with heart disease are prone to depression, while depression can lead to heart disease.

Both depression and heart disease are leading causes of disability [12]. The impact of comorbidity of those two diseases has been highlighted in a landmark study demonstrating that the risk of cardiac death in the 6 months after acute myocardial infarction is about 4 times greater in patients with depression compared to those without [13]. The publication of this study in 1993 stimulated further research to determine the impact of depression on cardiac outcomes [10]. Now, depression is known as a predictive factor of poor outcomes after myocardial infarction, including recurrence, cardiac death and all causes of death. Depression increases mortality 2.3-fold times after myocardial infarction [14], 1.8-fold times in congestive heart failure [15], 3.3-fold

times in unstable angina [16], and 2.4-fold times after coronary artery bypass [17]. A Japanese study comparing depression, anxiety, and anger reports that depression in hospitalized cardiovascular patients is a stronger independent risk factor for adverse cardiac events than either anxiety or anger [18]. In addition to the health risks, the comorbid condition is costly, imposing high out-of-pocket burdens on these patients. The out-of-pocket expenditure burden is estimated to double in patients who suffer from both heart disease and psychological distress compared to that in patients with heart disease only [19].

Possible Mechanisms of the Link between Heart Disease and Depression

Many mechanisms have been proposed to explain the link between heart disease and depression from basic science to the epidemiological level. Many studies have suggested that biological, psychosocial, and behavioral factors are related to the association between heart disease and depression [20]. Although the mechanism underlying this relationship remains not fully understood, these efforts help generate possible intervention strategies.

Biological factors

Biological factors representing a possible link between heart disease and depression include (A) neuroendocrine dysregulation, (B) inflammation, and (C) enhanced platelet activation and endothelial dysfunction. In addition to its effects during the acute phase of heart disease, prolonged stress activates the hypothalamic-pituitary-adrenal (HPA) axis and releases cortisol. High levels of cortisol deplete collagen, counteract insulin, decrease bone density and weaken the immune system, often resulting in various health conditions and diseases. On the other hand, a strong association exists between depression and increased cortisol. A previous study revealed that highly stressed women with cardiovascular disease have a 1.6-fold greater risk (95%CI: 1.3-2.2) compared to those without stress [21].

Meta analyses suggest that inflammation may also be a link between heart disease and depression. Depression and C-reactive protein (CRP), interleukin (IL)-1, and IL-6 are positively associated in both clinical and community populations [22]. CRP concentration is related to risks of coronary heart disease, ischemic stroke, and vascular mortality [23].

Platelet activation and endothelial dysfunction are other possible biological mechanisms that connect heart disease with depression. Depression increase susceptibility to blood clotting due to alterations in multiple steps of the clotting cascade, including platelet activation and aggregation [24]. D-dimer, von Willebrand factor and plasminogen activator inhibitor (PAI) levels are related to depression [25]. It is worth noting that treatment with sertraline in depressed patients after acute coronary syndrome is associated with reduced platelet/endothelial activation despite coadministration of antiplatelet regimens such as aspirin [26].

A decrease in nitric oxide (NO) availability would predispose patients to developing atherosclerosis [20]. The levels of both plasma NO metabolite (NOx) and platelet endothelial NO synthase (eNOS) activity are significantly lower in patients with major depression compared with healthy control subjects [27]. These results suggest that patients with depression are at risk for atherosclerosis; however, treatment with a serotonin and norepinephrine reuptake inhibitor (SNRI) (milnacipran) significantly increases the plasma NOx levels [28].

Another interesting topic is brain-derived neurotrophic factor (BDNF). There is a strong evidence that serum BDNF levels are abnormally low in patients with major depressive disorder and that the BDNF levels are elevated with antidepressant treatment [29]. BDNF also plays an important role in atherogenesis and plaque instability [30].

Psychosocial factors

The medical community has accepted that acute myocardial infarction and sudden cardiac death can be triggered by stressors such as heavy physical exertion and severe emotional stress [31], and the meta-analysis shows that depression is as a strong predictor of coronary heart disease [32]. The INTERHERT study, a large global standardized case control study, involving a sample of 24,767 patients in 52 countries, revealed that the presence of psychosocial stressors is associated with increased risk of acute myocardial infarction. The psychosocial stressors are ongoing work-related stress, ongoing home stress, ongoing general stress and financial stress [33]. The effect of psychosocial factors on cardiac function is likely greater than is commonly recognized, resulting in an increasing level of interest in this area.

An increased incidence of acute cardiac events has been reported in communities after stressful events. After the Great Hanshin Earthquake in Japan [34], increased numbers of patients were admitted to emergency departments due to myocardial infarction, and cardiovascular events increased among German supporters during the World Cup match [35]. These consequences clearly show the potential for acute and direct impacts of life events on the human autonomic nervous system.

Since the theory that "Type A" personality, that is, a compound of hostility, competitiveness and impatience, triggers heart attacks, was introduced in the United States in the late 1950s, the personality theory remained highly controversial in the scientific community. Although researchers in recent years have tended to deny any association between heart disease and personality, related constructs to those of the Type A personality are regaining attention. A systematic review in 2009 showed that anger and hostility increased risk of cardiovascular disease [36]. Recently, a new type of personality trait, the Type D, was found to increase the risk of cardiovascular events. The Type D personality was also linked to an increased risk of depression [37]. Biological and behavioral pathways are being studied to explain these adverse effects of the Type D personality on health.

Behavioral factors

Health risk behaviors including smoking, unhealthy diet, and physical inactivity contribute to risk factors of heart disease. These behavioral factors are also prevalent in patients with depression, including smoking [38], and lower levels of physical and social activities [39]. Nonadherence to medication is a risk factor for both adverse outcomes of depression and coronary heart disease [40].

Genetic determinants

Genetic connection is a new avenue of investigation to explain the link between heart disease and depression. An American study of 2,731 male-male twin pairs from the Vietnam Era Twin Registry suggests that 20% of genetic influence is common across heart disease and depression [41]. The Swedish population-based twin registry with 30,374 twins also shows the possibility of genetic factors to explain the relationship between major depression and coronary heart disease [11]. The serotonin transporter gene

(*5-HTTLPR*) polymorphism is related to both emotion and platelet activation and is, therefore, a promising candidate as a genetic determinant of linked heart disease and depression [20]. Carriers of the s allele of *5-HTTLPR* are considered to be more vulnerable to depression in patients with heart disease [42].

Therapeutic Approaches

Medications

Treatment options for depression include antidepressants, cognitive behavioral therapy, and physical activity. The American Heart Association (AHA) recommends SSRI or SNRI as the first-line treatment for moderate to severe depression [43]. There is strong evidence of the safety of the SSRI, sertraline in particular. Sertraline has shown no significant adverse effects in patients with coronary heart disease in the Sertraline Antidepressant Heart Attack Randomized Trial [44]. Citalopram was also recommended as a first-line agent based on a randomized trial; however, in 2012, the US Food and Drug Administration has warned of drug-induced QTc interval prolongation and *torsade de pointes* when using citalopram at doses greater than 40 mg per day (http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm) .

One of the challenges to treating depression in patients with heart disease is that cardiologists must decide whether to use antidepressants as primary treatment. In fact, depression in patients with heart disease is often left untreated, or the best treatment is often not provided. It is also true in reality that there are various barriers to coordinating with the liaison consultation psychiatrist in clinical settings. Even though the cardiologist consults with the psychiatrist, advice from the psychiatrist is often limited to advocating for the temporary discontinuation of psychotropic agents.

New cardiac and psychotropic agents are constantly being introduced into practice. Although the safety of each drug is assessed, every possible combination with other drugs cannot be evaluated. In addition, polypharmacy is common in psychiatric patients as well as in elderly patients, while cardiologists and primary care physicians have more opportunities to prescribe psychotropic medications for comorbid patients. These trends increase the potential risk of drug-drug interaction, but no consensus exists regarding cardiac drug interactions with concurrent psychotrophic prescriptions. Strain et al. conducted a series of studies on the drug combinations among cardiologists, psychiatrists and experts in clinical pharmacology since the 1990s [45-47]. They systematically reviewed commonly prescribed cardiac and psychotropic medications, and rated the level of significance in interaction between cardiac drugs and psychotropic drugs as "major" (potentially life-threatening or capable of causing permanent death), "moderate" (a deterioration in a patient's status, resulting in additional treatment or hospitalization or extension of hospital stay), or "minor" (bothersome or unnoticeable) [45, 47]. In 2002, the review was updated with newly added drugs [47].

Table 1 shows 15 drug combinations that would increase the risk of serious adverse events. Five of the 15 combinations include tricyclic antidepressants. Combination therapy with tricyclic antidepressants may cause fatal ventricular arrhythmia, *torsade de pointes*, due to prolongation of QT interval with ibutilide, and interference with brethylium's effects, and may potentiate the pressure effects of direct acting sympathomimetics (e.g., dobutamine, norepinephrine, epinephrine, and phenylephrine) while decreasing the pressor response to indirect-acting sympathomimetics (e.g., dopamine) [45]. Tricyclic antidepressants have antiarrhythmic effects, and therefore are contraindicated after myocardial infarction [48].

Table 1. Major drug-drug interactions between cardiac and psychotropic agents

Cardiac agents	Psychotropic agents
Adenosine	Carbamazepine
Amiodarone	Trazodone
Atorvastatin	Nefazodone
Bretylium	Tricyclic antidepressants (desipramine, doxepin, imipramine)
Clonidine	Tricyclic antidepressants
Diuretics	Lithium
Furosemide	Fluoxetine
Ibutilide	Phenothiazines/Haloperidol
Ibutilide	Tricyclic antidepressants
Quinidine	Selective serotonin reuptake inhibitors (SSRIs)
Quinidine	Tricyclic antidepressants
Sympathomimetics (dobutamine, dopamine, amphetamines, ephedrine, phenylephrine)	MAO inhibitors
Sympathomimetics (dobutamine, norepinephrine, epinephrine, phenylephrine)	Tricyclic antidepressants
Warfarin	Barbiturates

This table is a summary of the 1999 [45] and 2002 [47] studies by Strain et al.

SSRIs are generally safe, but combining them with furosemid or quinidine requires caution. When furosemid and fluoxetine are co-administered, there is a risk of hyponatremia. Concurrent use of quinidine and an SSRI inhibits metabolic enzyme, and thus the plasma concentration and side effects of both agents should be observed. Drug-drug interactions newly added in 2002 include atorvastatin and nefazone, and warfarin and barbiturates. Because both combinations affect the metabolism of cardiac agents, plasma concentrations of atorvastatin and warfarin should be observed [47]. The data are still limited, and so the risks and benefits of psychotropic agents should be carefully balanced, and potential drug-drug interactions should be closely monitored. Good quality studies are needed to establish standard medication protocols in comorbid patients with depression and heart disease.

Cognitive behavioral therapy

The Harvard research group conducted a large multicenter randomized controlled trial, the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study in 2,481 patients with myocardial infarction receiving treatment for depression with cognitive behavioral therapy and SSRIs. The intervention has not been found to reduce cardiovascular events or mortality, although depression and social isolation are improved [49]. Since that study appeared, no large-scale clinical trial has

been conducted regarding cognitive behavioral therapy in patients with heart disease. A *post hoc* subgroup analysis of ENRICHD during the 29-month follow-up period has revealed a significant reduction in mortality and morbidity in depressed post-myocardial infarction patients receiving SSRIs [50].

Physical activity

The potential benefits of exercise for improving cardiovascular fitness [51] and reducing depressive symptoms [52] have been emphasized in recent studies. Since depression may be a barrier to participating in exercise programs, health care providers should facilitate patient participation in exercise programs tailored to patients' cardiac conditions.

Collaborative care

The results of two studies published in 2010 deserve attention. One described patient-centered management based on guidelines provided by nurses for patients with depression and chronic disease that has shown to improve both depression and chronic disease [53], and the other described collaborative care ("enhanced depression care") for patients with coronary syndrome that has shown to improve depression and cardiac prognosis with a high level of patient satisfaction [54].

Katon et al. conducted a single-blind, randomized, controlled trial in 14 primary care clinics to examine depression management and improvement of glycemic/hypertension/lipid control in 214 participants with poorly controlled diabetes mellitus, coronary heart disease, or both and coexisting depression [53]. The 12-month intervention included self-care support and medication for depression, hyperglycemia, hypertension, and hyperlipidemia. The target goal was determined among the patient, nurse, and the primary care physician. The nurse coordinated care between the primary care physician and a psychiatrist, and played a central role in intervention. The patient visited the clinic 2 or 3 times a week, while the nurse supervised the patient weekly.

Collaborative care is an established program in primary care [55]. It consists of: (A) an enhanced care approach, with treatment delivered by a clinical nurse specialist, psychologist, social worker, and/or psychiatrist; (B) the patient's choice of psychotherapy and/or pharmacotherapy; (C) problem-solving therapy (psychotherapy); (D) a stepped-care approach with reviews of symptom severity and treatment; and (E) a standardized instrument used to track depressive symptoms. Davidson et al. applied this approach to patients with coronary syndrome [54].

In contrast to Berkman et al. who conducted a cross-sectional study in patients with major depression or minor depression [49], Davidson et al. limited the participants in their study to those with persistent depressive symptoms (a Beck Depression Scale score being greater than 10 for more than 3 months). It was a successful strategy to have a specific target population.

In the United Kingdom, the National Institute of Clinical Excellence (NICE) recommends a stepped care model for the treatment of depression [56]. Stepped care provides a framework for the care of patients with chronic illnesses, including hypertension, diabetes mellitus, and depression with the least costly, least intensive, and least restrictive treatment. The care is tailored based on severity, clinical status, and patient preference. The least intensive care includes self-care support, and care can be intensified to cognitive behavioral therapy, medication management, and hospital care (Table 2).

Table 2. Stepped care*

	Targets	Treatments (examples)
Step 1	All known and suspected presentations of depression	Assessment, support, psycho-education, active monitoring
Step 2	Persistent sub-threshold depressive symptoms; mild to moderate depression	Step 1 plus Low-intensity psychosocial interventions, psychological interventions, medication
Step 3	Persistent sub-threshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions; moderate and severe depression	Step 2 plus high-intensity psychological interventions, combined treatments, collaborative care
Step 4	Severe and complex depression; risk to life; severe self-neglect	Step 3 plus , electroconvulsive therapy, crisis service, combined treatments, multi-professional and inpatient care

* National Institute for Health and Clinical Excellence: *Depression in Adults with a Chronic Physical Health Problem: Treatment and Management*. London: British Psychological Society and Gaskell, 2010 [56].

Patient Participation

According to a systematic review, no single intervention has been found to be effective for reducing 30-day rehospitalization in patients with chronic disease; but discharge planning, follow-up telephone call, and patient-centered discharge instructions have shown promising results in combined intervention [57]. Another systematic review found that case management and collaborative care (telephone and in person) can improve medication adherence for more than one condition, particularly in patients with depression [58]. This evidence suggests that patients' views are essential for effective interventions. An interesting systematic review supports that the detection of depression during physical illness must take into account the patients' beliefs and the integration of depression management with management for risk factors for cardiovascular disease [59]. Psychiatric liaison-consultation should be established in the department of cardiology, and training of coordinators who work between cardiologist and psychiatrist is needed for enhanced patient care.

Conclusion

There is a growing interest in the connection between heart disease and depression. Despite the extensive studies of this subject, much remains inconclusive because the association is complex and multifaceted. Depression in patients with heart disease is often overlooked and remains untreated. As health care becomes more specialized and fragmented, these comorbid patients are increasingly at risk to receive suboptimal care. Bridging the gap between cardiology and psychiatry is essential. Psychiatrists can play a vital role in improving mental health of patients with heart disease.

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