Fulyzaq（商品名は Crofelmer）[10]が抗ウイルス治療を受けている HIV/AIDS 患者の非感染性下痢に対して承認されている。しかし,「TCM 製品」の医薬品としての承認はまだなされていない。「TCM 製品」としては，2010年8月に天津天士力集団の複方丹参滴丸（心臓・脳血管疾患薬）[11]が，2013年1月に血脂康（高脂血症薬）[12]が FDA の Phase2 を終了したと報道されている。

米国における「TCM 製品」には，DSHEA 法（Dietary Supplement Health and Education Act of 1994）[13]に従い，Dietary Supplement として，申請・登録がなされて販売されているものがある。DSHEA 法では，パッケージ表示のやり方を定めているが，それに従っていない製品もあり，Dietary Supplement として登録されずに販売されているものもあるようである。

米国の ISO 代表団の代表は American Herbal Products Association（AHPA）の会長であり，会員会社からも数社が ISO 会議に参加している。AHPA の中には Chinese Herbal Products Committee が設けられており，その活動内容は "Promotes responsible commerce of those herbs and herbal products that are included in and/or based on traditional use of Chinese herbs" となっている。AHP の会員の中で「TCM 製品」に関係する会社は20社あり，内訳は，Botanical Supplier3社，Distributor 5社，Finished Product Marketer: Consumers 3社，Finished Product Marketer: Professionals 1社，Manufacturer 6社，Educational Institution 2社となっている[14]。この Manufacture には「TCM 製品」以外を取り扱っている会社もあり，6社全てが「TCM 製品」を製造しているかどうかはわからないが，少なくとも数社は「TCM 製品」の製造を行っている事が確認できている。したがって，米国は，「TCM 製品」の消費国であるとともに，製造国という側面も有している。

5）ヨーロッパにおける「TCM 製品」

ヨーロッパでは，植物薬の伝統があり，古くより，植物性医薬品が用いられてきている。欧州薬局方（EP）にも多数の生薬が収載されており，人参など，日本や中国で使用されている生薬もある。

2004年4月に，EU では植物薬に関する承認制度 Traditional Herbal Medicine Registration Scheme（THMRS）が開始された。この制度以前に欧州で販売されていた植物薬は2011年4月末までは OTC 薬として販売できるが，それ以後は，有効性のエビデンス（EU の中での15年間の使用経験，世界的な30年の使用経験）がないと，市場から撤退させられることになった。この条件をクリアした西洋系の植物薬は多数あったが，中成薬でこの条件をクリアしたものはわずか1製品（地奥心血康カプセル[15]）であり，その他の全ての中成薬は欧州市場から締め出されることとなった[16]。このことにより，2012年1-7月期，中国の対 EU の中薬輸出額は，前年同期比で36.5％も下落した[17]。なお，EU で通常の医薬品（market authorization）として承認された「TCM 製品」はない。現在，EU 諸国で，合法的に流通している「TCM 製品」は，地奥心血康カプセルを除いては効能のない刻み生薬や，調剤用の単味生薬エキスだけである。

2. TC249 WG2 設立の経緯

2010年6月中国・北京で開催された ISO/TC249 第1回 Plenary meeting においては医療機器（鍼を含む）と天然物の品質と安全性分野の新規提案（New Work Item Proposal）を作成するタスクフォースを組織し，ドイツが責任国となることが決定された。

2011年5月にオランダ・ハーグで開催された第2回 Plenary meeting においては，この医療機器と天然物の品質と安全性分野の標準を同一の専門

家（Expert）で作成していくことは難しいことから，まず，医療機器領域と天然物領域とに分けて議論することになった。次いで，天然物領域に関して，今後，どのように標準を作成していくかについて議論がなされた。この議論の参加国は，日本，中国，韓国，ドイツ，米国，カナダ，オーストラリア，オランダ，南アフリカ，タイの10ヵ国であった。最終的には生薬を担当するWG1（議長国：中国）と，工業製品（加工調整を含む）を担当するWG2（議長国：ドイツ）とに分けて議論していくこととなった。

ハーグ会議で，WG1，2が設立され，その分担領域が決定されたものの，両者の担当領域は一連のものであり，その境界線は明確にはなっていなかった。この2つのWGのうち，まず，WG1が2011年12月に中国・北京で開催され，WG1の担当領域に関する議論がなされた。当初は，議長は，農産物を採取，収穫するところまでがWG1の担当領域であるとしていたが，議論の中で，生薬の加工調整や，刻み生薬の品質（指標成分や汚染物質，毒性物質）までWG1が担当するということが，WG1として決定された。

2012年4月にドイツ・ベルリンで開催されたWG2会議においては，このWG1の決定を受けて議論がなされたが，ハーグでの議決通り，WG2では生薬の加工調整も取り扱い，刻み生薬も工業製品の1つであることから，WG2で担当することがWG2として再確認された。

2012年5月の韓国・テジョンでの第3回Plenary meetingでは，WG1とWG2との主張が矛盾することから調整が行われ，最終的には，WG1のタイトルとスコープは下記のようになった（WG2のタイトルとスコープは上述参照）。

Title: Quality and safety of raw materials and traditional processing

Scope: To create standards related to raw materials at any stage up to and including harvest of a plant ingredient and collection of an animal or mineral ingredient, and the traditional processing of raw materials.

3. WG2における標準提案の状況

WG2においては，現在3件の予備作業項目（PWI: Preliminary Work Item）が提案されている。

1）Quality and Safety of natural materials and manufacturing products made with natural materials used in and as traditional Chinese medicine (TCM)*（提案国：ドイツ）

本提案は，工業製品の品質と安全性を，原料（Starting materials）と最終製品（Finished products）との2つの段階で保証しようというものである。ドイツの主張では，この2つの段階で保証すれば十分であるとのことである。これは，ヨーロッパは「TCM製品」の製造国ではなく輸入国であることから，輸入された製品の保証をターゲットとした考え方である。

2）Quality and Safety of natural materials and manufacturing products made with natural materials used in and as traditional Chinese medicine (provisional)（提案国：日本）

日本の漢方・生薬製剤の品質保証も，当然，原料（生薬）と最終製品とで行われているが，これに加えて中間製品（エキス）での品質保証，製造工程における品質管理を加えることで，より完璧な品質保証となっている。日本としては，他国にもこのような品質保証の方法を推奨するため，ドイツの提案を補完するものとして，このPWIを提案している。

日本には，製造工程における品質管理として，業界の自主基準である漢方GMP[18]があり，最新版は2012年3月に改訂されたものである。この改訂は，日本がPIC/S（The Pharmaceutical

Inspection Convention and Pharmaceutical Inspection Co- operation Scheme）[19]に加盟申請するにあたり，PIC/SのAnnex 7 "Manufacture of herbal medicinal products"（最新版は2013年1月1日改訂版[20]）に対応するためである。また，中国でも医薬品GMPの付録として，中薬のGMPが存在する[21]。この他の国にも植物薬GMPのようなものがあり，これらを参考に，ISOとしての「TCM製品」の工程管理の保証を行おうとする提案である。

3) General requirements of manufacturing process for Red Ginseng（提案国：韓国）

韓国の主要輸出品の「TCM製品」であるコウジンの製造工程の標準化の提案である。

これら，3つの提案は2012年3月のWG2 web会議を経て，2012年5月の南アフリカ・ダーバンでの第4回Plenary meetingにおいて，新作業項目（NWIP: New Working Item Proposal）としての投票の承認を得る計画である。

WG2内では，各国のレギュレーションが異なることから，これらの標準には特定の方法，特定の規格値を盛り込まないことで，現時点では一致している。

また，第4回Plenary meetingには，韓国から"Therapeutic equivalence of single herb products for herbal decoction/preparation"，"Guidelines for manufacturing safe and regular herb preparations in individual clinics"の2件の提案がなされ，議論がなされる予定である。

さいごに

今まで，中国は5つのWGの中で，唯一WG2だけは標準化の新規提案を行っておらず，感心が低いように見える。ただ，2013年1月7日の中国中医薬報に掲載された記事[22]では，今後，中成薬の標準化を積極的に行うとともに，国際標準と，生薬や中成薬の各国の局方や法規との関係を処理していくことが述べられてしる。したがって，今後，中国からWG2に対し中成薬の標準化の提案が出される可能性がある。この中成薬の定義は現在のところ不明であるが，漢方製剤との関係で注意が必要である。今後も，日本国民の健康に悪影響が出ないよう，注意して活動していきたい。

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* リンク先は，2011年1月29日現在アクセス可能

シリーズ和漢　第3回

品質の「よい」漢方エキス製剤とは

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医療用漢方エキス製剤が、1976年に大量に保険収載されてから30年以上がたちます。皆さんの中には、病院薬剤師になられたときには、既に、医療用漢方エキス製剤が薬局にあったため、特別なものとは思っておられない方も多いと思います。

漢方エキスの品質規格が日本薬局方に収載されはじめたのは、実は、ごく最近の2006年の15局からです。従いまして、生薬の品質に関する教育は受けたことはあっても、漢方エキスの品質については教育を受けたことはないという方が多いのではないでしょうか。そこで、今回は、漢方エキス製剤の品質について、医療用漢方エキス製剤を中心に説明します。

漢方エキス製剤に求められる品質は、新薬とは同じではない

医薬品は有効で安全なものがよいということは、言うまでもないことです。医薬品では、その有効性と安全性が、どのロットでも均一であることが、当然、求められます。

単一化合物を有効成分（成分本質）とする、いわゆる新薬では、有効成分の純度を高め、不純物の割合を極力減らすとともに、GMPにより安全で安定した製造を行うことで、均一性を保証しているわけです。

漢方エキス製剤も医薬品ですので、基本的な考え方は同じです。しかし、新薬との大きな違いは、全ての含有成分が解明されていないことです。また、天産物を原料としているため、各含有成分量が全てのロットで完全に同じにはならないということです。したがって、漢方エキス製剤の品質は、新薬とは、別の観点からも考える必要があります。

甘草の有効成分はグリチルリチン？

「甘草の主成分はグリチルリチンである」と、よく、言われます。皆さんもそのように習われたと思います。しかし、甘草の煎液中のグリチルリチンを定量しても数%にすぎません。「甘草の主成分はグリチルリチンである」とは、「甘草の知られている成分の中で、甘草に特異的でかつ定量可能な（低分子）物質のうちで量が多いものはグリチルリチンである」というのが本当の意味です。甘草からのグリチルリチンの単離は古くから行われており、グリチルリチンを用いた薬効研究も多く行われてきたため、その多様な作用が動物において数多く報告されています。そのため、「甘草の有効成分はグリチルリチンである」と言われる場合が多いのですが、正しくは「甘草の有効成分の“ひとつ”はグリチルリチンである」と言うべきでしょう。もし、甘草の有効成分がグリチルリチンだけであるのなら、甘草を含有する漢方エキス製剤では、原料として甘草を用いる必要はなく、グリチルリチンを配合すればよいことになります。甘草の大部

分を占めるグリチルリチン以外の成分（低分子物質だけでなく、多糖類やタンパクなども含む）は、全ては同定されておらず、それらが、甘草が含有される漢方エキス製剤の薬効に全く無関係であるとは言えませんので、現在も、漢方製剤の原料としては、グリチルリチンではなく甘草が用いられているわけです。「よい」品質の漢方エキス製剤とは、グリチルリチンのような特定のひとつの物質の量だけが多ければよいということではありません。

品質をコントロールする

皆さんがスイカを食べられる時、毎回、同じ甘さであったということはないでしょう。今回はアタリ、今回はハズレと、一喜一憂されている方もおられると思います。同じ農家が同じ年に作ったスイカでも、常に 100%同じ味であるということはありえません。収穫してから熟すまでの時間も、味に影響があるでしょう。このようなことは、天産物を原料としている漢方エキス製剤にも当てはまります。スイカでしたら、「今回はハズレか」ですみますが、医薬品である漢方エキス製剤では、「今回は効きが悪かった」、「今回は効きすぎた」、「今回は副作用が多かった」ではすみません。

漢方製剤の品質を、全ロットで 100%同じにすることはスイカ同様、不可能です。ただ、ある一定の範囲の中におさめることはできます。欧米も含め、植物製剤においては “Quality Control” という言葉をよく使いますが、これは、完全に同一なものを求めるのではなく、一定の範囲の中で、ばらつきのない製品を作ろうという考え方です。

従って、「よい」品質の漢方エキス製剤とは、いつ、どのロットの製品を用いても、大きな差のない有効性、安全性が担保されているもの、ということになります。

現在の漢方エキス製剤の品質規格

1976 年に医療用漢方エキス製剤が大量に保険収載された直後は、その品質や 1 日製剤量中のエキス量は各社の判断で決められていました。しかし、1981 年頃から、富山医薬大の薬剤部などから、1 日製剤量中の特定物質の量がメーカーによって大きくばらつくことが学会で報告されるようになりました。これらの報告を受け、国の方でも漢方エキス製剤の品質が問題になり、1982 年-1984 年に厚生科学研究「漢方エキス製剤の規格基準作成に関する研究」が行われました。そして、この研究結果をもとに、1985 年 5 月に厚生省薬務局審査課長通知 薬審 2 第 120 号「医療用漢方エキス製剤の取り扱いについて」が出され、各社は、原則 1 年以内に、医療用漢方エキス製剤の規格を、この通知にあわせて申請しなおすように求められました。この代替申請に当たっては、申請書の右肩に丸で囲った「漢」という文字を朱色で入れるように求められましたので、このことは、通称 “マル漢”と呼ばれています。この時の“マル漢”規格が、今日まで続く医療用漢方エキス製剤の品質であり、日本薬局方への漢方エキス収載のもとになった考え方です。したがって、“マル漢”以前の、医療用漢方エキス製剤を用いた臨床論文や学会報告は、同じ名前の処方の報告でも、現在の医療用漢方エキス製剤を用いたものではないということになります。なお、医療用漢方製剤の中には、一部、生薬末を混合しただけのもありますが、これらは、エキス剤ではないため、“マル漢”の対象にはなりませんでした。

“マル漢”で各メーカーが求められたことは、エキス製剤は、2 種類以上の管理指標成分を用いて、標準湯剤(土瓶などの古典的な製造方法で得られた湯液)との同等性を、一定の上下幅の中で担保する(一定の範囲内でのばらつきを認める)こと、1 日分の乾燥エキス量は 1 日分の煎液からとれるエキス全量とすること、というものでした。標準湯剤は、各社が、当時、自社で使用していた標準的な生薬をもとに作成しました。したがいまして、現在の各社の漢方エキス製剤の品質は、1985-1986 年頃に各社で用いていた生薬を用いて作成した煎じ薬の品質ということになります。それ以後、各社は、この規格で漢方エキス製剤を継続して製造していますので、一定の品質の漢方エキス製剤が供給できているということになります。“マル漢” により、漢方エキス製剤の全ての含有成分量が規定されたわけではありませんが、この考え方は、当時としては画期的なものであり、2006 年からの日本薬局方への漢方エキスの収載も、この考え方の延長線上にあります。ただし、日局への漢方エキスの収載に当たっては、定量法の科学的進歩にあわせて最適なものへ統一がなされ、また、管理指標成分の追加が行われています。なお、管理指標成分とは標準湯剤との同等性を保証するための成分であり、必ずしも“いわゆる有効成分”とは限りません。しかし、管理指標成分になる物質は、単離できる成分でもありますので、その薬理研究が行われやすく、その結果、いろいろな作用が報告されていますので、“有効成分のひとつ”とはいえるかもしれません。

漢方エキス製剤の品質は生薬の品質が決める

“マル漢”により、各社の医療用漢方エキス製剤の品質は規定されたものの、限られた数種の指標成分の量だけで漢方エキス製剤全体の均一性を保証してよいのかという意見もあるかと思います。当然、管理指標成分の定量だけで、製剤全体の均一性が保証されるわけではありません。“マル漢”自体は、同じ生薬を原料に用いた場合の、煎剤とエキス剤の同等性を保証したにすぎません。マル漢時の品質の漢方エキス製剤を継続供給するためには、管理指標成分値の同等性だけではなく、原料として一定の品質の生薬の使用が大前提になります。管理指標成分になっているグリチルリチンの漢方製剤中の含量をなるべく一定にするためには、グリチルリチンの含量がなるべく同じ甘草を原料に用いるということになりますが、これだけでは、単にグリチルリチンの含量が同じ製剤を作っていることになります。これでは、その他の成分はどうなっているかわかりません。生薬からの漢方エキス製剤の製造過程では、人為的に、特定の成分を増やしたり、減らしたりすることはできませんし、また、そのようなことは認められていません。つまり、一定の品質の漢方エキス製剤を作ろうとしたら、おのずと、一定の品質の生薬を集めなければならないということになります。ここにメーカーのノウハウがあるわけです。

品質が一定の生薬とは

それでは、一定の品質の生薬とはどのようなものでしょうか。現在、医療用漢方エキス製剤の原料である生薬の大部分は、日本薬局方で、その品質規格が定められています。特異成分含量に関しては、規定されているとしても大部分の生薬では1つだけです。その他の成分も一定に保とうとしたら、同じ基原植物を、同じ環境で栽培して、同じ時期に収穫して、同じよ

うに加工する、といったことが重要になります。一定の甘さのスイカを作るのと、考え方は同じです。市場に行って、どのスイカを買おうかと考えていただけでは同じ甘さのスイカを大量に揃えることは難しいですので、スイカの生産地に行って、栽培・加工方法を確認、指導することが、同じ甘さのスイカを揃えるためには必要です。すなわち、一定の品質の生薬を大量に入手しようとしたら、生薬市場で原料を買ってくるのではなく、契約栽培などを行い、生薬栽培にまで踏み込んで管理することが重要といえます。これを GAP: Good Agricultural Practice(採取までも含めると GACP: Good Agricultural & Collection Practice)と呼びます。漢方薬メーカーの中には、GAP を社内で規定して、栽培指導・管理に応用しているところもあります。

品質が一定の生薬から品質の一定の漢方エキス製剤を製造する

漢方エキス製剤の品質の大部分は生薬の品質が担っていますが、一定の品質の生薬からであっても、当然、一定の製造方法でエキス製剤を生産しないと一定の品質の漢方エキス製剤は作ることはできません。安定製造のためには、新薬では GMP を用いて製造することになります。ただ、GMP は、新薬を主な対象に作成されていますので、天産品を原料とする漢方エキス製剤では、十分でないところがあります。そこで、漢方/生薬メーカーからなる日本漢方生薬製剤協会では、医薬品 GMP の上乗せ基準である「生薬及び漢方生薬製剤の製造管理及び品質管理に関する基準」(一般には漢方 GMP と呼ばれる)を作成して、これに基づいて漢方製剤を製造しています。このことにより、一定の品質の生薬から一定の品質の漢方エキス製剤が製造できるわけです。

安全な製剤を供給する

薬剤師の皆様は、医薬品の安全性というと、副作用や相互作用のことを考えられると思いますが、製薬メーカーでは、これに加えて、製剤中の不純物の問題があります。特に漢方薬では、原料が天然物であることに起因する、新薬とは別の不純物の問題があります。この問題は、スイカなどの食物にも共通するものです。漢方製剤で問題になる不純物は、残留農薬、重金属・ヒ素、微生物の 3 つが主なものです。

残留農薬に関しては、一部の生薬に関して、日本薬局方で BHC, DDT の限度値が決められています。また、日本漢方生薬製剤協会では、一部のエキス製剤で、有機塩素系、有機リン系、ピレスロイド系の残留農薬の限度値を自主基準として定めています。ただ、これらだけでは、心配される方が多いというのが現状ですので、メーカーによっては、自主的に、これに上乗せした残留農薬の自主基準値を決めてチェックしています。当然、この限度値をこえたものは市場には出ず、廃棄処分となるわけですが、メーカーとしては、「はい、これは限度値を超えたので捨てましょう」というものが続出したのでは大変です。そこで、購入する生薬の残留農薬の量を事前にチェックした上で購入する、あるいは、栽培地において、使用する農薬の種類、量、使用時期を指導するということになります。モトから断った方が、メーカーにとっては、安心で安全な上に経済的ということになります。

重金属・ヒ素についても日本薬局方で、生薬、漢方エキスについて限度値が定められてい

ます。これらは、生薬に用いる植物が生育する土壌由来ですので、栽培管理で減らすことはできません。そのため、重金属・ヒ素の汚染の少ない土地で栽培された生薬を選んで購入するとか、汚染の少ない土地で自社栽培するということになります。

微生物に関しても、日本薬局方の参考情報で限度値が定められています。漢方エキスは富栄養物で、かつ、吸湿性が高いため、微生物が発生しやすいものです。この値を一定以下にするためには、エキスや製剤の製造方法、保管などが重要なファクターになります。調剤用の漢方エキス製剤(いわゆるボトル品)に関しては、保管条件によっては、開封後に微生物が増えることもあり得ますので、適切な保管をお願いします。

トレーサビリティ

時々、野菜に生産者の顔写真や名前のシールがはってあることがありますが、このように、食品の分野では、生産物の流通過程をたどれることをトレーサビリティと呼んでいます。漢方エキス製剤も一種の農産物ですので、同じ考え方が必要です。皆さんが調剤される漢方エキス製剤のロット番号から、それを作った工場、指標成分の値や汚染物質の値などはもちろんのこと、原料として使用された生薬、さらにその生薬がどこの畑でとれて、どのような方法で栽培されたものか、生産した人は誰か、そこまで把握できて、はじめて漢方エキス製剤の資格を有していると言ってもよいでしょう。

さいごに

以上、品質の「よい」漢方エキス製剤とは何かについて述べてきました。漢方メーカーでは、畑から皆様の手元に届くまで、上記のように細心の注意を払って、漢方エキス製剤を生産しているわけです。現在の漢方エキス製剤の品質評価の方法は完璧ではありませんが、現在の科学で行えることは全て行っているとも言えます。今後、さらなる科学の進歩に伴い分析方法が改良されたりして、漢方エキス製剤の品質の考え方も変わっていくものと思われます。漢方メーカーは、古臭い会社と思われがちですが、実は、常に積極的に新しい技術を追いかけているものなのです。

会報編集委員会より

今回、シリーズ和漢第3回の原稿を執筆いただきました株式会社ツムラの新井一郎先生は富山大学薬学部の卒業生、高城副会長の同級生であり、123 号の巻頭言を執筆いただきました三村先生の研究室のご先輩です。今回の依頼に快く執筆を引き受けてくださいました。この場をかりて感謝申し上げます。

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Complementary Therapies in Medicine

Effectiveness of animal-assisted therapy: A systematic review of randomized controlled trials

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KEYWORDS
Animal-assisted therapy;
Systematic review;
Randomized controlled trials

Summary The objectives of this review were to summarize the evidence from randomized controlled trials (RCTs) on the effects of animal-assisted therapy (AAT). Studies were eligible if they were RCTs. Studies included one treatment group in which AAT was applied. We searched the following databases from 1990 up to October 31, 2012: MEDLINE via PubMed, CINAHL, Web of Science, Ichushi Web, GHL, WPRIM, and PsycINFO. We also searched all Cochrane Database up to October 31, 2012. Eleven RCTs were identified, and seven studies were about ''Mental and behavioral disorders''. Types of animal intervention were dog, cat, dolphin, bird, cow, rabbit, ferret, and guinea pig. The RCTs conducted have been of relatively low quality. We could not perform meta-analysis because of heterogeneity.

In a study environment limited to the people who like animals, AAT may be an effective treatment for mental and behavioral disorders such as depression, schizophrenia, and alcohol/drug addictions, and is based on a holistic approach through interaction with animals in nature.

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To most effectively assess the potential benefits for AAT, it will be important for further research to utilize and describe (1) RCT methodology when appropriate, (2) reasons for non-participation, (3) intervention dose, (4) adverse effects and withdrawals, and (5) cost.

Contents

Introduction

Animals have been our companions since ancient times, and we are well aware of the many ways that some of them have aided us throughout history.[1] Animals are used to help humans in ways; for example, serving as working shire horses and guide dogs for the blind.[2] The modalities that use animals as tools for improving physical, mental and social functions, and educational and welfare aspects of humans are called animal-assisted interventions (AAI).

To understand the different types of AAI and integrate some useful definitions, we accepted the classification of the American Veterinary Medical Association (AVMA).[3] The AVMA classifies AAI into three category: (i) animal-assisted

activities (AAA) that utilize companion animals, (ii) animal assisted-therapy (AAT) that utilizes therapy animals, and (iii) service animal programs (SAP) that utilize service animal. Especially, AAT is a goal-directed intervention in which an animal that meets specific criteria is an integral part of the treatment process. These programs are usually directed and delivered by human health or human services professionals with specialized expertise and within the scope of practice of their profession.

A pioneer systematic review (SR) of AAT showed that overall it was associated with moderate effects in improving outcomes in four areas: autism-spectrum symptoms, medical difficulties, behavioral problems, and emotional well-being.[4] However, contrary to expectations, characteristics of the SR participants and studies did not produce differential outcomes. Some limitations of the SR were that it only included articles published prior to 2004, and it did not include randomized controlled trials (RCTs).

It is well known in research design that evidence grading is highest for a SR with meta-analysis of RCTs. Although many studies have reported the effects of AAT,[1,4,5] there is no SR of the evidence based on RCTs. Therefore, the objective of this review was to summarize the evidence from RCTs on the effects of AAT.

Methods

Criteria for considering studies included in this review

Types of studies
Studies were eligible if they were RCTs.

Types of participants
There was no restriction on participants.

Types of intervention and language
Studies included at least one treatment group in which AAT was applied. The definition of AAT in this study was based on the classification of the AVMA.[3] Type of animal was not a restriction but we excluded robotic animals (e.g., robotic dog). There was no restriction on the basis of language.

Types of outcome measures
We focused on all cure and rehabilitation effects using the International Classification of Diseases-10 (ICD-10).

Search methods for identification of studies

Bibliographic database
We searched the following databases from 1990 up to October 31, 2012: MEDLINE via PubMed, CINAHL, Web of Science, Ichushi Web (in Japanese), the Global Health Library (GHL), the Western Pacific Region Index Medicus (WPRIM), and PsycINFO. We also searched the Cochrane Database of Systematic Reviews (Cochrane Reviews), the Database of Abstracts of Reviews of Effects (DARE), the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Methodology Register (Methods Studies), the Health Technology Assessment Database (Technology Assessments), the NHS Economic Evaluation Database (NHS EED), The Cochrane Collaboration databases (Cochrane Groups), and the Campbell Systematic Reviews (the Campbell Collaboration) up to October 31, 2012. All searches were performed by a specific searcher (hospital librarian) who was qualified in medical information handling, and who was sophisticated in searches of clinical trials.

Search strategies
The special search strategies contained the elements and terms for MEDLINE, CINAHL, Web of Science, Ichushi Web, GHL, WPRIM, PsycINFO, and All Cochrane databases (Table 1). Only keywords relating to the intervention were used for the searches. Titles and abstracts of identified published articles were reviewed in order to determine the relevance of the articles. References in relevant studies and identified RCTs were screened.

Registry checking
We searched the International Clinical Trials Registry Platform (ICTRP), the International Prospective Register of Systematic Review (PROSPERO), the Clinical Trials.gov registry, and the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR) up to October 31, 2012. ICTRP in the WHO Registry Network meets specific criteria for content, quality and validity, accessibility, unique identification, technical capacity and administration. Primary registries meet the requirements of the ICMJE. Clinical Trials.gov is a registry of federally and privately supported clinical trials conducted in the United States (US) and around the world. UMIN-CTR registers clinical trials conducted in Japan and around the world.

Handsearching, reference checking, and other
We handsearched abstracts published in AAT and relevant journals in Japan. We checked the references of included studies for further relevant literature.

Review methods

Selection of trials
In order to make the final selection of studies for the review, all criteria were applied independently by four authors (e.g., TH, JK, SP, and SO) to the full text of articles that had passed the first eligibility screening (Fig. 1). Disagreements and uncertainties were resolved by discussion with other author (e.g., HK, KT, and YM).

Studies were selected when (i) the design was a RCT and (ii) one of the interventions was a form of AAT. Protocols without results were excluded, and we included only completed studies. Cure and rehabilitation effects were used as a primary outcome measure. Trials that were excluded were presented with reasons for exclusion (Appendix).

Table 1 The special search strategies.

1. MEDLINE
   #1 Search (''Animal Assisted Therapy'' [Mesh] OR Animal Assisted Therap*)
   #2 Search (''animals, domestic'' [Mesh] OR domestic animal*)
   #3 Search (''bonding, human-pet'' [Mesh] OR companion animal*)
   #4 Search ((#1) OR #2) OR #3
   #5 Search (Randomized Controlled Trial[pt] or Multicenter Study[pt] or Controlled Clinical Trial[pt] or Randomized Controlled*)
   #6 Search (#4) AND #5 Filters: Publication date from 1990/01/01; Humans; English; Japanese
2. CINHAL
   #1 (MH ''Animal Assisted Therapy (Iowa NIC)'')
   #2 ''animal assisted'' AND therap*
   #3 (MH ''Pet Therapy'')
   #4 (MH ''Human-Pet Bonding'')
   #5 S1 OR S2 OR S3 OR S4
   限定 - 出版日 (開始): 19900101-; 人間; 言語: English, Japanese; 出版物タイプ: Clinical Trial, Journal Article, Randomized Controlled Trial 検索モード - 入力した語順どおりに検索
3. Web of Science
   TS=(''animal assisted'' AND therap*) OR TS=(''animal-assisted'' AND therap*) OR TS=''animal NEAR/1 therap*''
   絞込込み: 言語 = (ENGLISH) AND ドキュメントタイプ=(ARTICLE)
   データベース=SCI-EXPANDED タイムスパン=1990-01-01 - 2012-10-31
   活用語処理=オン
4. Ichushi Web
   #1 動物活用療法/TH or 動物活用/AL or アニマルセラピー/AL
   #2 人間と動物のきずな/TH
   #3 乗馬/TH or 乗馬/AL
   #4 #1 or #2 or #3
   #5 (#4) and (DT=1990:2012 PT=原著論文)
5. Global Health Library
   Search: animal assisted therap* in title
   Limit: English (Language)
6. WPRIM
   #1 Abstract:animal% and Abstract:therap% -Limits:1990-2012; Humans
   #2 All:animal assisted therapy or All:animal-assisted
   #3 #1 or #2
7. PsycINFO
   (SU.EXACT.EXPLODE(''Animal Assisted Therapy'') OR (''Animal Assisted Therapy'' OR ''Animal Assisted Therapies'')) AND (rtype.exact(''Journal'' OR''Journal Article'') AND la.exact(''English'' OR ''Japanese'') AND po.exact(''human'' OR ''inpatient'' OR ''outpatient'') NOT rtype.exact(''Review-book'' OR ''Editorial'' OR ''Comment/reply'' OR ''Letter'') NOT me.exact(''Literature Review'')) AND pd(>19900101)
8. All Cochrane
   #1 MeSH descriptor: [Animal Assisted Therapy] explode all trees
   #2 ''animal assisted'' or ''animal-assisted'' (Word variations have been searched)
   #3 MeSH descriptor: [Animals, Domestic] explode all trees
   #4 ''domestic animal*'' (Word variations have been searched)
   #5 MeSH descriptor: [Bonding, Human-Pet] explode all trees
   #6 ''companion animal*'' (Word variations have been searched)
   #7 #1 or #2 or #3 or #4 or #5 or #6
9. Campbell Systematic Reviews
   Search for: animal* in ''ALL text'' AND therap* in ''ALL text''
10. ICTRP
    animal asssited
11. International Prospective Register of Systematic Reviews
    animal assisted therapy [in All fields] OR animal [in Interventions/Exposure]
12. Clinical Trials. gov
    [Basic Search]: animal assisted
13. UMIN-CTR
    動物介在 in「自由記載語」OR animal therapy in「自由記載語」OR アニマルセラピー in「自由記載語」

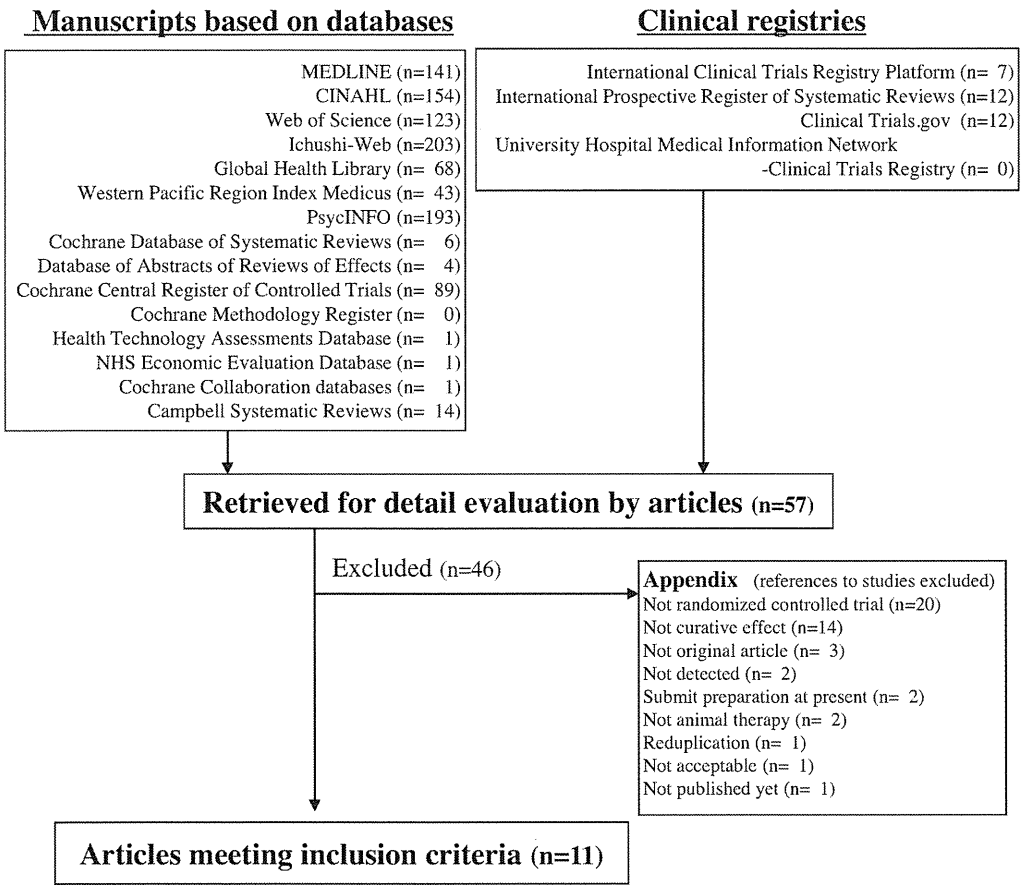

Figure 1 Flowchart of trial process.

Risk of bias (quality) assessment

In order to ensure that variation was not caused by systematic errors in the study design or execution, three review authors (HO, SP, and TH) independently assessed the quality of articles. A full quality appraisal of these papers was made using the Cochrane's criteria list for the methodological quality assessment.[6] Disagreements and uncertainties were resolved by discussion with other authors (e.g., HO, SO, and HK).

Each item was scored as 'yes' (y), 'no' (n), 'do not know or unclear' (?), or 'not applicable' (n/a). Depending on the study design, some items were not applicable. The "n/a" was excluded from calculation for quality assessment. We displayed the percentage of present description on all 11-check items for the quality assessment of articles. Then, based on the percentage of risk of poor methodology and/or bias, each item was assigned to the following categories: good description (80—100%), poor description (50—79%), or very poor description (0—49%). Inter-rater reliability was calculated on a dichotomous scale using percentage agreement and Cohen's kappa coefficient (k).

Summary of studies and data extraction

Ten review authors (HP, HO, SH, TO, SP, TA, TH, JK, SO and HK) described the summary from each article based on the recommended structured abstracts.[7,8]

Benefit, harm, and cost

The GRADE Working Group[9] reported that the balance between benefit and harm, quality of evidence, applicability, and certainty of the baseline risk were all considered in judgments about the strength of recommendations. Adverse events (harm) and cost for intervention were especially important information for researchers and users of clinical practice guidelines, and we presented this information with the description of each article.

Analysis

Pre-planned stratified analyses were: (a) trials comparing AAT with no treatment or waiting list controls, (b) trials comparing different types of general rehabilitation methods (e.g., physical therapy, occupational therapy), and (c) trials comparing AAT with other different intervention(s). We expressed the results of each RCT, when possible, as relative risk (RR) with corresponding 95 percent confidence intervals (95%CI) for dichotomous data, and as standardized or weighted mean differences (SMD) with 95%CI for continuous data. Heterogeneous results of studies that provided by inclusion criteria were not combined.

Research protocol registration

We submitted and registered our research protocol to the PROSPERO database (no. CRD42012003032),[10] an

international database of prospectively registered SRs in health and social care. Key features from the review protocol are recorded and maintained as a permanent record in PROSPERO. This provides a comprehensive listing of SRs registered at inception, and enables comparison of reported review findings with what was planned in the protocol. PROSPERO is managed by CRD and funded by the UK National Institute for Health Research (NIHR). Registration was recommended because it encourages full publication of the review's findings and transparency in changes to methods that could bias findings.[11]

Results

Study selection

The literature searches based on databases included potentially relevant articles (Fig. 1). Abstracts from those articles were assessed, and 57 papers were retrieved for further evaluation (checks for relevant literature). Forty-six publications were excluded because they did not meet the eligibility criteria (see Appendix). Eleven studies[12–22] met all inclusion criteria (Table 1).

Study characteristics

The language of all eligible publications was English. Target diseases and/or symptoms (Table 2) were schizophrenia,[12,19,20] cancer,[13] advanced heart failure,[14] depression,[15,21] ambulatory motor impairment,[16] older adults admitted to skilled rehabilitation units,[17] elderly persons with chronic psychiatric, medical, and neurologic conditions,[18] and a mental illness diagnosis as well as a history of alcohol/drug abuse or other addictive behaviors.[22]

Based on ICD-10, we identified a disease targeted in each article (Table 3). Among 11 studies, seven studies were about "Mental and behavioral disorders (F10-19,[22] F20,[12,19,20] F30-33,[15,21] and the unidentified due to including many geriatric disease[18])". There was one study each in "Neoplasms (C00-D48; the unidentified due to many site of cancer)",[13] "Diseases of the circulatory system (I50.1)",[14] and "Injury, positioning and certain other consequences of external causes (T90-93)".[16] Because there were a variety of target diseases, there was one article that we could not identify a single disease.[17]

Types of animal studied included dog,[12–14,16,18,19] dog or cat,[20] dolphin,[15] bird,[17] cow,[21] and dog, rabbit, ferret, and guinea pig.[22]

In a study for inpatients with schizophrenia,[12] compared with the control group, the dog treatment group showed significant improvement on all measures expect for social support and negative psychiatric symptoms. The results of the study showed that AAT can promote significant improvements in many clinical aspects among inpatients with schizophrenia. Similarly, in a study for inpatients with schizophrenia,[19] the dog intervention group showed significant improvements in the living skill profile, social contact score, and in the positive and negative symptom dimensions. On the other hand, the control group also showed significant positive changes in positive and general symptoms. No differences were found between the two groups before and after the application of the intervention. As for elderly schizophrenic patients, a controlled 1-year study provided subjects with their own dog or cat as the intervention animal, according to personal preference.[20] The Social Adaptive Functioning Evaluation (SAFE) scores at termination of the study showed significant improvement compared with baseline scores, and were significantly more positive for the AAT group on both Total SAFE score and on the Social Functions subscale.

A study tried to identify to what extent an AAT (i.e., visits with a dog) affects mood, self-perceived health, and sense of coherence among patients undergoing radiation therapy for cancer.[13] Results showed no statistically significant differences within or between groups in mood, sense of coherence, or two facets of self-perceived health.

An AAT was performed in patients hospitalized with heart failure.[14] The study tried to determine whether a 12-min hospital visit with a therapy dog improves hemodynamic measures, lowers neurohormone levels, and decreases state anxiety in patients with advanced heart failure. Compared with controls, the volunteer-dog group had significantly greater decreases in systolic pulmonary artery pressure and pulmonary capillary wedge pressure during and after the intervention.

A study based on dolphins was performed to evaluate the effectiveness of animal facilitated therapy with dolphins, controlling for the influence of the natural setting, in the treatment of mild to moderate depression.[15] For the participants who completed the study, the mean severity of the depressive symptoms was more reduced in the treatment group than in the control group.

A study reported the effectiveness of dog intervention for people with severe ambulatory disability.[16] Significant positive changes in all but two dependent measures were associated with the presence of a service dog both between and within groups. Psychologically, all participants showed substantial improvements in self-esteem, internal locus of control, and psychological well-being within six months after receiving their dog. Socially, all participants showed similar improvements in community integration. Demographically, all participants showed increases in school attendance and/or part-time employment. Economically, all participants showed dramatic decreases in the number of both paid and unpaid assistance hours.

An avian interventional study was performed to examine the alleviation effect on depression, loneliness, and morale of older adults in skilled rehabilitation units.[17] In the presence of a companion bird, the experimental group showed a significant decrease in depression, but no decrease in morale or loneliness was observed in the control group that was without a bird.

A dog interventional study was performed to evaluate the effects on geriatric psychiatry inpatients.[18] No significant differences in the Multidimensional Observation Scale for Elderly Subjects scores were found between or within groups before and after the interventions. There was a non-significant tendency for subjects who received the dog intervention to have less irritable behavior after treatment. However, women with dementia who received either pet therapy or exercise intervention had improved irritable behavior scores after treatment.

Table 2 Brief summary of articles based on structured abstracts and additional elements.

Reference no.	12	13	14
Author	Chu CI, et al.	Johnson RA. et al.	Cole KM. et al.
Citation	J Psychosocial Nurs 2009;47:42–49	Oncology Nursing Forum 2008;35:225–232.	Am J Crit Care 2007;16:575–585
Title	The effect of animal-assisted activity on inpatients with schizophrenia	Animal-assisted activity among patients with cancer: effects on mood, fatigue, self-perceived health, and sense of coherence	Animal-assisted therapy in patients hospitalized with heart failure
Aim/objective	To evaluate the effects of animal-assisted activity on self-esteem, control over activities of daily living, and other psycho-physiological aspects among Taiwanese inpatients with schizophrenia	To identify to what extent an animal-assisted activity (i.e., visits with a dog) affects the mood, self-perceived health, and sense of coherence among patients undergoing radiation therapy.	To determine whether a 12-min hospital visit with a therapy dog improves hemodynamic measures, lowers neurohormone levels, and decreases state anxiety in patients with advanced heart failure
Setting/place	Psychiatric institution in Hualien Country, located in eastern Taiwan	Outpatient radiation therapy units of two hospitals in a mid-sized, midwestern city, USA	The cardiac care unit or the cardiac observation unit
Participants	30 adult patients with schizophrenia	30 adult patients undergoing nonpalliative radiation therapy	76 adult patients with a diagnosis of advanced heart failure
Intervention	Weekly 50-min animal-assisted activity sessions were arranged for the patients of the treatment group over a period of 2 months. Patients in the control group received treatment as usual. The animal-assisted activity was held in the hospital's garden but took place in the activity hall during inclement weather and during the first 2 weeks of the study so as not to distract the patients. The animals used in this study were two healthy, friendly, medium-sized, trained dogs of nonspecific breeds. They were provided by trainers, but during interactions with patients were accompanied only by the investigators	Patients participated in 15-min sessions three times per week for four weeks. Dog visit group: Two visitor dogs used in the study were certified by the College of Veterinary Medicine at the University of Missouri Pet-assisted Love and support (PALS) program. Dogs were selected for quiet temperaments, friendliness with strangers, and length of visitation experience. During the sessions, participants combed, petted, played, and talked with the dog. The dog handlers introduced the dog to the participant during first session and were instructed to avoid conversation with the participants. Friendly human visit group: Participants met individually with the same adult. Friendly human visitors were volunteer nursing students, emeritus nursing faculty, hospital administrative staff from other departments, and community members. Reading group: Participants read silently researcher-provided magazines. Magazines were selected based on lack of content related to health and fitness, cancer and treatments, selfhelp, counseling, pets, AAA, and animal-assisted therapy	Patients randomly assigned to the experimental group received a visit from a volunteer and a dog. The type of dog breed was not controlled for; 14 dogs of 10 various breeds were used. The 14 dogs included 1 extra-large dog, 6 large dogs, 5 medium dogs, and 2 small dogs. Each visit was conducted according to the guidelines taught during the volunteer and dog orientation: (1) volunteer introduces self and dog, (2) patient washes his or her hands before the visit, (3) dog lies on the bed with its head within 0.6 m (2 ft) of the patient's head on a clean sheet used as a barrier to the patient's bed, (4) patients may pet the dog and talk to the dog and volunteer and (5) patient washes his or her hands after the visit. No attempt was made to control the content of the conversation during the visit. The visit lasted for 12 min. After the visit, an instant self-developing photograph was taken of the patient with the dog and given to the patient. Patients randomly assigned to the volunteer-only group received a 12-min visit from a volunteer. The volunteer introduced himself or herself, sat in a chair approximately 1.2 m (4 ft) from the patient's head, and let the patient know that the visit would last for 12 min if the patient was up to it. No attempt was made to control for the volunteer's usual conversation during the visit. No patient requested to end any earlier than 12 min. Patients randomly assigned to the control group were asked to lie quietly without talking unless they had a specific need or request. For all groups, a sign was placed on the patient's door or curtain asking everyone to please not interrupt the visit. Nurses assigned to patients to provide care were asked not to interrupt during the 12-min interaction and data collection, unless an emergency occurred. Volunteers participating in the volunteer-dog teams were used for the volunteer-only group as much as possible to minimize any influence of a volunteer's personality on the results. For all groups, data were collected at baseline immediately before the visit, 8 min after the intervention started, and at 16 min, which was 4 min after the end of the visit
Main and secondary outcomes	Self-esteem, self-determination, extent of social support and increases and decreases in adverse psychiatric symptoms	Mood:Profile of Mood States (POMS), Self-perceived health:Self-perceived health questionnaire, Sense of coherence:Orientation to Life Questionnaire(OTLQ), Exit questionnaire: Participants completed this five-item tool that was developed by the research team	Heart rate, cardiac index, plasma levels of catecholamines, and anxiety
Randomization	No description	Via a computer-generated random-numbering system	Using a table of random numbers
Blinding/masking	No description	No description	Data collectors did not speak to the patients during the measurement of outcome variables and the intervention
Numbers randomized	Treatment group ($n=15$) and control group ($n=15$)	The dog visit group (treatment group) ($n=10$), friendly human visit group ($n=10$), or quiet reading group ($n=10$)	Volunteer-dog team group ($n=26$), volunteer only group ($n=25$), and control group ($n=25$)
Recruitment	The participants in this study were patients selected from a 600-bed psychiatric institution in Hualien County, located in eastern Taiwan	28 Caucasian and 2 African American adults with no known pet allergies who were beginning nonpalliative (first-line) radiation therapy for cancer for a period of at least four weeks following initial diagnosis	76 adults patients with a diagnosis of advanced heart failure admitted to the cardiac care unit or the cardiac observation unit
Numbers analyzed	Treatment group ($n=12$) and control group ($n=15$)	The dog visit group (treatment group) ($n=10$), friendly human visit group ($n=10$), or quiet reading group ($n=10$)	Volunteer-dog team group ($n=26$), volunteer only group ($n=25$), and control group ($n=25$)

Table 2 (*Continued*)

Outcome	Compared with the control group, the treatment group showed significant improvement on all measures except for social support and negative psychiatric symptoms. The results of this study showed that animal-assisted activity can promote significant improvements in many clinical aspects among inpatients with schizophrenia	No statistically significant differences were found within or between groups in mood, sense of coherence, or two facets of self-perceived health. However, participants described each of the three activities as beneficial	Compared with controls, the volunteer-dog group had significantly greater decreases in systolic pulmonary artery pressure during (−4.32 mm Hg) and after (−5.78 mm Hg) and in pulmonary capillary wedge pressure during (−2.74 mm Hg) and after (−4.31 mm HG) the intervention. Compared with the volunteer-only group, the volunteer-dog group had significantly greater deceases in epinephrine levels during (−15.86 pg/mL) and after (−17.54 pg/mL) and in norepinephrine levels during (−232.36 pg/mL) and after (−240.14 pg/mL) the intervention. After the intervention, the volunteer-dog group had the greatest decrease from baseline in state anxiety sum score compared with the volunteer-only (−6.65 units) and the control groups (−9.13 units)
Harm	Three patients who were afraid of dog did not participate in the animal-assisted activity	No dog allergy	No description
Conclusion	Animal-assisted activity should be integrated into the treatment of institutionalized patients with schizophrenia	This study was one of few involving AAA (animal-assisted activity) among patients with cancer in a randomized design. One issue that may have affected the findings of present study is that disease progression during the time of the intervention was not measured. Side effects of radiation therapy were not assessed. Further research is needed with larger samples to identify whether the effects are statistically recognizable	Animal-assisted therapy improves cardiopulmonary pressures, neurohormone levels, and anxiety in patients hospitalized with heart failure
Trial registration	No description	No description	No description
Fund	Nothing	No description	Grant 01061809 from the Pet Care Trust Foundation, Quilcene, Washington
Cost of intervention	No description	Dog visits are no more costly than human visits because all organizations provide dog visits on a volunteer basis	No description
	15	16	17
Author	Antonioli C, et al.	Allen K, et al.	Jessen J, et al.
Citation	BMJ 2005;331	JAMA 1996;275:1001–1006	Psychological Reports 1996;78:339–348
Title	Randomised controlled trial of animal facilitated therapy with dolphins in the treatment of depression	The value of service dogs for people with severe ambulatory disabilities	Avian companionship in alleviation of depression, loneliness, and low morale of older adults in skilled rehabilitation units
Aim/objective	To evaluate the effectiveness of animal facilitated therapy with dolphins, controlling for the influence of the natural setting, in the treatment of mild to moderate depression and in the context of the biophilia hypothesis	To assess the value of service dogs for people with ambulatory disabilities	To examine the effect of a caged bird on depression, loneliness, and morale of older adults in skilled rehabilitation units
Setting/place	The study was carried out in Honduras, and recruitment took place in the United States and Honduras	Environments of study participants	Two skilled rehabilitation units in Nebraska
Participants	Outpatients, recruited through announcements on the internet, radio, newspapers, and hospitals	Forty-eight individuals with severe and chronic ambulatory disabilities requiring use of wheelchairs who were recruited from advocacy and support groups for persons with muscular dystrophy, multiple sclerosis, traumatic brain injury, and spinal cord injury	40 older adults in a skilled rehabilitation unit, self-reported measures of depression, loneliness, and morale

Intervention	Participants were asked to play, swim, and take care of the animals. They had an introductory session, to explain about dolphin behavior and water safety. The first part of the trial, which took half an hour, was structured so the participants could familiarize themselves with the animals. Participants were standing in the water, close to the trainer. The dolphin, following the trainer's signals, performed trained behaviors (such as a jump or a swim). Participants were able to touch the dolphins when close to the trainer. The second part of the trial, another half an hour, was unstructured, and free and spontaneous interactions occurred. Participants were snorkeling in the water with the dolphins. In the control group, participants were assigned to an outdoor nature program featuring the same water activities as the animal care program but in the absence of dolphins, to control for the influence of water and other, non-specific, environmental factors. In the outdoor nature program, participants had to swim and snorkel in the barrier coral reef for 1 h a day and had a similar degree of individualized human contact as in the animal care program. Participants were informed of the marine ecosystem, the barrier coral reef (the second largest in the world after the great barrier reef of Australia), and water safety. Both programs were run simultaneously and lasted for a period of two weeks for each group. The treatments were given daily, Monday to Friday, 1 h per day	Individuals assigned to the experimental group received assistance dogs 1 month after the study began (in 1990), and subjects in the wait-list control group 12 months later (13 months after the study began). Dogs were made available to participants in this study through trainers dedicated to providing dogs to people with disabilities. All the dogs were initially raised in family environments to socialize them. The dogs then entered training designed to teach them how to provide general assistance. Following this, each dog was paired with a person with a disability and was given individualized special training to expand the dog's commands to meet the unique needs of the person to whom it was assigned and to ensure that the person with a disability learned to handle the dog effectively	A bird was placed in the room of each subject in the experimental group. Care for the birds was provided either at times the subject was not in the room or by having a staff member bring the bird and cage out of the room so that there was no intervention by the investigator through interaction with the subject. The control group had no intervention other than their routine care in the unit. At the end of 10 days, the three instruments were administered again to all subjects (post-test), and the bird was removed. Although a relatively short time period, 10 days was the maximum amount of time it could be predicted that a sufficiently large sample would still be in the institution
Main and secondary outcomes	Hamilton rating scale for depression, the Beck depression inventory, and the Zung self rating anxiety scale	Self-reported assessments of psychological well-being, internal locus of control, community integration, school attendance, part-time work status, self-esteem, marital status, living arrangements, and number of biweekly paid and unpaid assistance hours	Morale, depression, and loneliness
Randomization	Random number table to generate the block allocation sequence	Individuals were matched on several characteristics, including age, sex, marital status, race, and the nature and severity of the disability, to create 24 pairs. Within each pair, individuals were randomly assigned to either the experimental or the wait-list control group	No description
Blinding/masking	The allocation sequence was concealed until treatments were assigned. We kept the randomization sequence hidden from the investigators giving the treatments by using a set of opaque numbered sealed envelopes, each containing the allocation for one patient	No description	No description
Numbers randomized	Animal care program group ($n = 15$) and outdoor nature program group ($n = 15$)	Experimental group ($n = 24$) and wait-list control group ($n = 24$)	Experimental group ($n = 20$) and control group ($n = 20$)
Recruitment	Field research work took place at the Roatan Institute for Marine Sciences (Roatan, Bay Islands, Honduras) between July 2002 and December 2003. After participants had read the information, we asked them for a medical certificate from their treating therapist	Qualifying individuals from New York, Pennsylvania, Massachusetts, and Connecticut were contacted through advocacy support groups (for example, the Muscular Dystrophy Association, the Multiple Sclerosis Association)	A sample of older adults admitted to two midwestern, skilled rehabilitation units participated

Table 2 (*Continued*)

Numbers analyzed	Animal care program group ($n=13$) and outdoor nature program group ($n=12$)	Experimental group ($n=24$) and wait-list control group ($n=24$)	Experimental group ($n=20$) and control group ($n=20$)
Outcome	Of the 30 patients randomly assigned to the two groups of treatment, two dropped out of the treatment group after the first week and three withdrew their consent in the control group after they had been randomly allocated. For the participants who completed the study, the mean severity of the depressive symptoms was more reduced in the treatment group than in the control group (Hamilton rating scale for depression and Beck depression inventory). For the sample analyzed by modified intention to treat and last observation carried forward, the mean differences for the Hamilton and Beck scores between the two groups was highly significant	Significant positive changes in all but two dependent measures were associated with the presence of a service dog both between and within groups. Psychologically, all participants showed substantial improvements in self-esteem, internal locus of control, and psychological well-being within 6 months after receiving their service dog. Socially, all participants showed similar improvements in community integration. Demographically, all participants showed increases in school attendance and/or part-time employment. Economically, all participants showed dramatic decreases in the number of both paid and unpaid assistance hours	With the presence of a companion bird, the experimental group ($n=20$) showed a significant decrease in depression compared to no decrease in morale or loneliness from the control group ($n=20$) who were without a bird
Harm	No description	No description	No description
Conclusion	The therapy was effective in alleviating symptoms of depression after two weeks of treatment. Animal facilitated therapy with dolphins is an effective treatment for mild to moderate depression, and is based on a holistic approach, through interaction with animals in nature	Trained service dogs can be highly beneficial and potentially cost-effective components of independent living for people with physical disabilities	Use of a companion bird may lessen negative effects of change of residence for older adults
Trial registration	No description	No description	No description
Fund	The Tursiops Society Onlus and the advice and support given by Andrew Weil and Brian Becker of the University of Arisona, USA; Stephen Kellert of Yale University, USA; and Costantino Balestra of the Universite Libre de Bruxelles, Belgium. We thank Yvonne Hartgers, Arnoldo Javier Montoya Stone, Aida Lagos, Hector Murcia Pinto for medical, phycological diagnosis and assistance; the research participants, the Psychiatric Hospital of Tegucigalpa and Roatan Hospital	No description	No description
Cost of intervention	No description	Total calculated costs of initial canine training at $10,000, lost investment income on initial training costs at 5% per annum compounded quarterly; $1000 per year in animal maintenance; an expected canine service period of 8 years; and $8, $10, and $12 per hour for paid human assistance	No description
Reference no.	18	19	20
Author	Zisselman MH, et al.	Villalta-Gil V, et al.	Barak Y, et al.
Citation	The American Journal of Occupational Therapy 1996;50:47–51	Anthrozoos 2009;22:149–159	Am J Geriatr psychiatry 2001;9:439–442
Title	A pet therapy intervention with geriatric psychiatry inpatients	Dog-assisted therapy in the treatment of chronic schizophrenia inpatients	Animal-assisted therapy for elderly schizophrenic patients
Aim/objective	To evaluate the effects of pet therapy on geriatric psychiatry inpatients	To assess the effectiveness of including a trained therapy dog in an intervention program applied to institutionalized patients with chronic schizophrenia	To evaluate the effects of AAT on long-stay geriatric schizophrenic patients in a controlled 1-year study
Setting/place	The 26-bed Wills Eye Hospital Geriatric Psychiatric Unit in Philadelphia	Saint John of God-Mental Health Services Hospital	The word of Kibbutz Givat Haim Ichud, Israel
Participants	Elderly persons with chronic age-related psychiatric, medical, and neurologic conditions such as depression, dementia, Parkinson's disease, stroke, and accompanying medical disorders	No description	20 adult patients with schizophrenia

Intervention	Intervention was provided for 5 consecutive days for each group. The intervention for the experimental group consisted of a 1-h visit with dogs. The subjects had contact with and fed the visiting dogs, were encouraged to reminisce about their own experiences with pets and other animals, and heard a brief talk about the dogs. The control group exercised for 1 h a day while the experimental group was visiting with the dogs. Adherence to both treatments of the subject's daily schedule remained the same. Additionally, all subjects continued receiving their psychotropic medications and individual and group psychotherapy sessions	The intervention program was applied by a trained psychologist. It consisted of 25 sessions of 45 min each; two sessions were given per week. The intervention group with therapy dog (LG + D) was directed by the psychologist, who was assisted by a two-year-old, female Labrador, certified as a therapy dog. The dog was accompanied by her handler. The group without a dog (lG) was directed by the same psychologist. The intervention was based on Integrated Psychological Treatment (IPT) designed by Brenner et al. (1994). This treatment for patients with schizophrenia has been developed to work as much on cognitive functioning as on social functioning. It is a group intervention structured program with five subprograms: cognitive differentiation, social perception, verbal communication, social skills training, and interpersonal problem solving. They are hierarchically ordered, so the first interventions are directed to basic cognitive skills, the next interventions transform the cognitive skills into social and verbal behaviors, and the last ones train the patients in the solution of more complex interpersonal problems. Sessions for the Lg + D group were designed so that the handler interacted with the dog and the therapist, the therapist interacted with the patient and the handler, and patients interacted with the dog and therapist. This design was used in order to minimize interactions between handler and patients, as the handler was not present in the lG group	AAT was undertaken once weekly on the same day. The therapists and assisting animals came to the ward at 10:30 am, and the group session lasted 3 h. Three AAT counselors from the PET (Pet Enrichment Therapy) program at Kibbutz Givat Haim Ichud, Israel, were regularly accompanied by a psychiatric nurse, providing a ratio of 1:2.5 caretakers to patients. Each patient was provided with his own dog or cat, according to personal preference. Sessions included ''ADL modeling activities'' such as petting, feeding, grooming, bathing, and teaching the animals to walk on a lead for greater mobility. Control-group patients were assembled for reading and discussion of current news for a similar duration on the same days that AAT was undertaken. These sessions were conducted by three certified nurses so as to keep the ratio of staff to patients equal to that of the AAT group
Main and secondary outcomes	Self-care functioning, disoriented behavior, depressed or anxious mood, irritable behavior, and withdrawn behavior	Symptoms, social competence, and subjective perception of quality of life. A schedule assessing adverse reactions to animals, the Wechsler Adult Intelligence Scale, and the Mini Mental State Examination were used as screening instruments, in order to confirm inclusion of patients into the sample.	Social-Adaptive Functioning Evaluation (SAFE)
Randomization	No description	24 patients with chronic schizophrenia were randomly selected from a computerized register	No description
Blinding/masking	The nursing staff member was also blind to group assignments	All patients were evaluated by a trained psychologist blind to the patient's intervention group at baseline and after the intervention program (patients were asked not to mention details about the therapy sessions and the psychologist was also not supposed to gather information about their intervention group)	Assessor (clinical psychologist)
Numbers randomized	Per therapy intervention ($n = 33$) or an exercise intervention ($n = 25$)	Intervention group with therapy dog ($n = 12$) and control group without a dog ($n = 12$)	Animal assisted treatment group ($n = 10$) and control group ($n = 10$)
Recruitment	Elderly persons with chronic age-related psychiatric, medical, and neurologic conditions such as depression, dementia, Parkinson's disease, stroke, and accompanying medical disorders	Only those patients staying at Long Term Care facilities were included; these patients cannot live in the community, due to their social and clinical characteristics. A long course of the disorder and cognitive or social deficits characterizes patients staying in these facilities	Subjects in the study were 20 chronic schizophrenic patients, who were long-stay residents at the Abarbanel Mental Health Center, Bat Yam, Israel