"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。

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

CrossMark

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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.

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_ド - 入力した語順どお込に検索

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_タベ_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_/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_ in 「自由記載語」
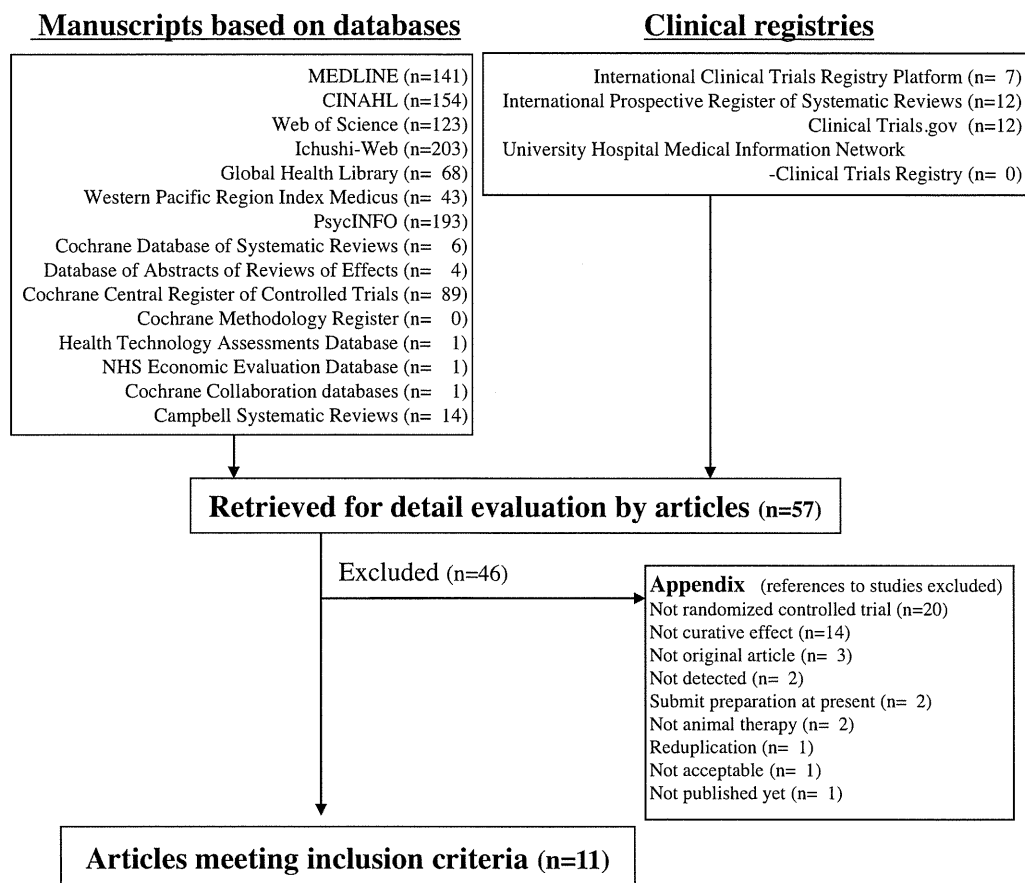
Manuscripts based on databases

MEDLINE (n=141)
CINAHL (n=154)
Web of Science (n=123)
Ichushi-Web (n=203)
Global Health Library (n= 68)
Western Pacific Region Index Medicus (n= 43)
PsycINFO (n=193)
Cochrane Database of Systematic Reviews (n= 6)
Database of Abstracts of Reviews of Effects (n= 4)
Cochrane Central Register of Controlled Trials (n= 89)
Cochrane Methodology Register (n= 0)
Health Technology Assessments Database (n= 1)
NHS Economic Evaluation Database (n= 1)
Cochrane Collaboration databases (n= 1)
Campbell Systematic Reviews (n= 14)

Clinical registries

International Clinical Trials Registry Platform (n= 7)
International Prospective Register of Systematic Reviews (n=12)
Clinical Trials.gov (n=12)
University Hospital Medical Information Network
-Clinical Trials Registry (n= 0)

Retrieved for detail evaluation by articles (n=57)

Excluded (n=46)

Appendix (references to studies excluded)
Not randomized controlled trial (n=20)
Not curative effect (n=14)
Not original article (n= 3)
Not detected (n= 2)
Submit preparation at present (n= 2)
Not animal therapy (n= 2)
Reduplication (n= 1)
Not acceptable (n= 1)
Not published yet (n= 1)

Articles meeting inclusion criteria (n=11)

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

Table 2 (*Continued*)

Numbers analyzed	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 = 9)	Animal assisted treatment group (n = 10) and control group (n = 10)
Outcome	No significant differences in the Multidimensional Observation Scale for Elderly Subjects (MOSES) scores were found between or within groups before and after the interventions. There was a nonsignificant tendency for subjects who received the pet 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	Patients in the IG + D group showed significant improvements in the LSP social contact score, in the positive and negative symptom dimension and total score of the PANSS, and in quality of life related with social relationships. Patients in the IG group showed significant positive changes in positive and general symptoms and total PANSS score. No differences were found between the two groups before and after the application of the intervention	The Social Adaptive Functioning Evaluation scores at termination 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
Harm	No description	Nothing	No description
Conclusion	This pilot study demonstrates the need for further research on animal-assisted interventions with hospitalized elderly persons. Differential improvement in women with dementia also requires further investigation	Introducing a dog into the psychosocial intervention for patients with schizophrenia produced some positive outcomes. However, the results of the study are not conclusive and must be interpreted cautiously	AAT proved a successful tool for enhancing socialization, ADLs, and general well-being
Trial registration	No description	No description	No description
Fund	A grant from Sandoz/Jeffs Companion Animal Center	The financial help of the La Caixa Foundation and was supported by the Spanish Ministry of Health, Instituto de Salud Carlos lll, CIBERSAM. The authors declare that no competing interests exist	No description
Cost of intervention	No description	No description	No description
Reference no.		21	22
Author		Pedersen I, et al.	Carolyn AM, et al.
Citation		Anthrozoos 2012;25:149—160	Anthrozoos 2000;13:43—47
Title		Farm animal-assisted intervention for people with clinical depression: a randomized controlled trial	Animal-assisted therapy in psychiatric rehabilitation
Aim/objective		To examine potential changes in mental health in people with clinical depression, while working with farm animals as the only task on the farm	To evaluate whether patients in the animal-assisted therapy group would show a greater increase in observed appropriate social behaviors than the control group patients who did not receive animal-assisted therapy
Setting/place		Eleven dairy farms from six different counties in Norway	Terrell State Hospital, Terrell, Texas
Participants		28 adult patients with clinical depression	69 inpatient participants at a large state psychiatric facility
Intervention		The intervention consisted of work and interaction with farm animals twice a week for 12 weeks. The time for each session spent on the farm per day varied from 1.5 to 3.0 h due to differences in farm size, degree of mechanization, and the amount of work. A first introductory visit was used by the participants to get familiar with the farm and farmer. On the following visit, the participants worked together with the farmer in the cowshed. The participants were allowed to choose work such as grooming, mucking, feeding, taking care of the calves, and milking. They could also choose to spend their time in physical contact with the animals. The participants did not take part in any other work at the farm	The experimental AAT group had animals visit the class each day. The animals included dogs, rabbits, ferrets, and guinea pigs. The animals remained for the entire class period and were moved from patient to patient. Patients in the group were allowed to observe the animals or interact with the animals – hold them, pet them, and/or play with them as long as they did not disrupt the group. Patients were not required to participate directly with any animals; such participation was voluntary and the patients determined the level of individual involvement. However, there was only one female patient out of all of the AAT subjects that elected to not interact directly with the animals

Main and secondary outcomes	Depression anxiety, and self-efficacy	Social Behavior Scale
Randomization	The randomization was conducted by a researcher blinded to farm and participants	No description
Blinding/masking	No description	It was not possible to keep the rater blind to condition since the behavior observations were made daily while the group was being conducted. However, neither those conducting the class nor the rater was privy to the design or intent of the study, and hence they remained essentially ''blind''. Data entry was by an individual who was also blind to the treatment conditions
Numbers randomized	The intervention group ($n = 16$) and the control group ($n = 13$)	Animal-assisted therapy group ($n = 18$) and control group ($n = 19$)
Recruitment	Thirty-five participants were recruited through advertisements, invitation letters from the Norwegian Labour and Welfare Service, and contact with health personnel. Potential participants received a letter describing the intervention, and the possibility to be allocated to either a control or an intervention group was stated	There were 69 inpatient participants (70% male and 30% female) at a large state psychiatric facility
Numbers analyzed	The intervention group ($n = 16$) and the control group ($n = 13$)	Animal-assisted therapy group ($n = 18$) and control group ($n = 19$)
Outcome	A significant decline in depression and a significant increase in self-efficacy were seen in the intervention group between recruitment and of intervention. In the control group, no significant changes were found. No significant differences were found when comparing change in mental health measures in the intervention and control groups. However, more subjects in the intervention group (6) than in the control group (1) had clinically significant change, indicating that animal-assisted intervention in Green care could be beneficial for subgroups of clients and act as a useful supplement within mental health care	Animal-assisted therapy patients interacted more with other patients. Similarly, there was a main effect for weeks, with improvement in scores over time but no interaction between weeks and groups. There was a similar finding for the AAT group; patients smiled and showed pleasure significantly more often than the control group patients and thus improved over the four weeks with no interaction between weeks and groups
Harm	No description	No description
Conclusion	Those who participated in animal-assisted therapy experienced statistically significant changes in depression and generalized self-efficacy. Although the changes were not significantly different from those in the control group, more participants in the intervention could be beneficial for subgroups of clients and act as a useful supplement within mental health care	These data suggest that AAT plays an important role in enhancing the benefits of conventional therapy and demonstrates the benefit of including a non-AAT group for comparison. The study also demonstrates the importance of using longitudinal, repeated measure designs. Previous studies may have failed to find significant effects because they were restricted to shorter intervals for measuring outcomes
Trial registration	No description	No description
Fund	A grant from the Research Council of Norway, and Agricultural Agreement	No description
Cost of intervention	No description	No description

Table 3 International classification of target diseases in each article.

Chapter	ICD code	Classification	Reference no. (detail ICD code)
1	A00-B99	Certain infectious and parasitic diseases	
2	C00-D48	Neoplasms	13 (the unidentified due to many site of cancer)
3	D50-D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	
4	E00-E90	Endocrine, nutritional and metabolic diseases	
5	F00-F99	Mental and behavioral disorders	12,19–20 (F20), 15,21 (F30-33), 18 (the unidentified due to including many geriatric diseases), 22 (F10-19)
6	G00-G99	Diseases of the nervous system	
7	H00-H59	Diseases of the eye and adnexa	
8	H60-H95	Diseases of the ear and mastoid process	
9	I00-I99	Diseases of the circulatory system	14 (I50.1)
10	J00-J99	Diseases of the respiratory system	
11	K00-K93	Diseases of the digestive system	
12	L00-L99	Diseases of the skin and subcutaneous tissue	
13	M00-M99	Diseases of the musculoskeletal system and connective tissue	
14	N00-N99	Diseases of the genitourinary system	
15	O00-O99	Pregnancy, childbirth and the puerperium	
16	P00-P96	Certain conditions originating in the perinatal period	
17	Q00-Q99	Congenital malformations, deformations and chromosomal abnormalities	
18	R00-R99	Symptoms, signs and abnormal clinical and laboratory finding not elsewhere classified	
19	S00-T98	Injury, positioning and certain other consequences of external causes	16 (T90-93)
20	V00-Y98	External causes of morbidity and mortality	
21	Z00-Z99	Factors influencing health status and contact with health services	
22	U00-U99	Code for special purpose	
–	Unidentified	Because many illnesses were mixed, we could not identify it.	17

A unique study was performed to examine potential changes in mental health in people with clinical depression who were working with farm animals as the only task on a farm.[21] The intervention consisted of work and interaction with farm animals twice a week for 12 weeks. Those who participated in animal-assisted therapy experienced statistically significant changes in depression and generalized self-efficacy. Additionally, more participants in the intervention could have been beneficial for the subgroups of clients and served as a useful supplement within mental health care, although these changes were not significantly different from those in the control group.

A study evaluated whether patients such as those with a mental illness diagnosis as well as a history of alcohol/drug abuse or other addictive behaviors in the AAT group would show a greater increase in observed appropriate social behaviors than patients in the control group.[22] AAT patients interacted more with other patients. Similarly, there was a main effect that lasted for weeks, with improvement in scores over time but no interaction between weeks and groups. There was a similar finding for the AAT group; patients smiled and showed pleasure significantly more often than the control group and thus improved over four weeks, with no interaction between weeks and groups.

Quality assessment

We evaluated 11 items from the Cochrane's criteria list in more detail (Table 4). Inter-rater reliability metrics for the quality assessment indicated substantial agreement for all 121 items (percentage agreement 97% and $k = 0.939$).

This assessment evaluated the quality of how the main findings of the study were summarized in the written report. In general, there was a remarkable lack of execution and/or description in the concealment, blinding, and intention-to-treatment (ITT) analysis. The items for which the description was lacking (very poor; <50%) in many studies were as follows (present ratio; %): "Was the treatment allocation concealed?" (45%); "Was the patient blinded to the intervention?" (40%); "Was the care provider blinded to the intervention?" (27%); "Was the outcome assessor blinded

Table 4 Evaluation of the quality of methodology for each article.

No	Criteria list	Reference no.											Present description	
		12	13	14	15	16	17	18	19	20	21	22	No/11	Rate (%)
1	Was the method of randomization adequate?	?	y	y	y	y	y	?	y	n	y	?	7	64%
2	Was the treatment allocation concealed?	?	n	?	y	y	y	y	y	?	n	?	5	45%
3	Were the groups similar at baseline regarding the most important prognostic indicators?	y	y	y	y	y	y	y	y	y	y	y	11	100%
4	Was the patient blinded to the intervention?	?	n	?	y	y	y	n	n	n	n	y	4	40%
5	Was the care provider blinded to the intervention?	?	n	n	y	?	?	y	n	n	n	y	3	27%
6	Was the outcome assessor blinded to the intervention?	?	?	?	n	?	n	?	y	y	n	y	3	27%
7	Were cointerventions avoided or similar?	y	n	y	y	y	y	y	?	?	y	y	8	73%
8	Was the compliance acceptable in all groups?	y	y	y	y	y	y	y	y	?	y	y	10	91%
9	Was the drop-out rate described and acceptable?	y	y	y	y	n	n	y	y	y	n	y	8	73%
10	Was the timing of the outcome assessment in all groups similar?	y	y	y	y	y	y	y	y	y	y	y	11	100%
11	Did the analysis include an intention-to-treat analysis?	n	n	y	y	y	n	n	?	n	y	y	5	45%
	Present description no/11	5	5	7	10	8	7	7	7	4	6	9	—	—
	Rate (%)	45%	45%	64%	91%	73%	64%	64%	64%	36%	55%	82%	—	—

y, yes; n, no; ?, do not know or unclear; n/a, not applicable.

to the intervention?'' (27%); and ''Did the analysis include an ITT analysis?'' (36%).

Meta-analysis

There were three RCTs on schizophrenia and two RCTs on depression. We could not perform a meta-analysis because of heterogeneity by difference of outcome measurement and intervention method (e.g., in dog, and in dog or cat).

Adverse events

Two studies reported no adverse events,[13,19] and one study described three patients who were afraid of dogs and did not participate in the intervention.[12] There were no descriptions about adverse events in the other eight studies[14-18,20-22] (Table 2).

Costs of intervention

Two studies[13,16] described information about the cost of intervention (Table 2). Johnson et al. showed that dog visits were no more costly than human visits because all organizations provide dog visits on a volunteer basis.[13] Allen et al. showed that the total calculated costs of initial canine training was $10,000, lost investment income on initial training costs was 5% per annum compounded quarterly, animal maintenance was $1000 per year, the expected canine service period was 8 years, and paid human assistance ranged from $8 to $12 per hour.

Discussion

This is the first SR of the cure effectiveness of ATT based on RCTs. Our study is unique because it summarized the evidence for each target disease according to ICD-10 classification. We assume that this study will be helpful to researchers who want to understand the effect of ATT comprehensively, and it could provide indispensable information for the organization that is going to make the guidelines according to each disease.

Among the 11 RCTs that were identified, target diseases and/or symptoms included schizophrenia, depression, cancer, advanced heart failure, severe ambulatory

disability, older adults admitted to skilled rehabilitation units, elderly persons with chronic psychiatric, medical, and neurologic conditions, and a mental illness diagnosis, as well as a history of alcohol/drug abuse or other addictive behaviors, and intervention methods included various approaches such as dog, dolphin, bird, cat, cow, rabbit, ferret, and guinea pig.

Tendency of target disease and outcome

The most commonly reported target diseases were "Mental and behavioral disorders (F10-20, 30—33, and unclear)",[12,15,17—22] and the effect of AAT on these diseases was improved mental health (e.g., anxiety and mood), QoL, and social behavior. The main reason given in these articles for improved mental health was that the feeling and memory of an animal allowed the patient to be comfortable, pleasant, and happy. For example, Le Roux and Kemp[23] reported the following narrative comments by participants: "we talked to each other about the dog", "visits from the dog made me think about my own dog when I was young", and "at night I think about Pietie (the dog) and I smile". In studies about the effects of AAT on anxiety, discomfort, fear, and pain, AAT has been variably applied as an accessory treatment for persons with addictions such as alcohol/drug abuses[22] and as evasion of direct discomfort for undergoing medical treatment for cancer.[13]

The other reported target diseases were "Diseases of the circulatory system (I50.1)"[14] and "Injury, positioning, and certain other consequences of external causes (T90-93)".[16] The former evaluated hemodynamic parameters, cardiac index, and neurohormone levels as primary outcomes. The latter assessed psychological variables such as well-being, internal locus of control, and community integration. Improvements seen in these studies were mainly due to effects of buffering a person's reactivity to mental stressor[24,25] and providing a sense of comfort and safety, and diverting attention away from the immediate stressors to a more pleasurable and calming interaction.[26]

Validity of overall evidence based on quality assessment

Overall evidence and quality assessment
The Cochrane's list is the most important tool related to the internal validity of trials. In this SR, there were serious problems with the conduct and reporting of the target studies. Our review especially detected omissions of the following descriptions: method used to generate concealment, blinding, and ITT analysis. Descriptions of these items were lacking (very poor; <50%) in many studies.

In the Cochrane Review,[27] the eligibility criteria for a meta-analysis are strict, and for each article, heterogeneity and low quality of reporting must first be excluded. We could not perform a meta-analysis. Due to poor methodological and reporting quality and heterogeneity, there was insufficient evidence in the studies of AAT, and we are therefore unable to offer clearly any conclusions about the effects of AAT based on RCTs.

Moreover, the CONSORT 2010[28] and the CONSORT for non-pharmacological trials checklists[29] are relatively new, but it was shown that the study protocol description and implementation for AAT studies should be subjected to these checklists.

Overall evidence
Most importantly, a specific adverse effect or harmful phenomenon such as allergy or fear for animals was not clearly observed overall, although we should consider the limitations and biases of these findings in the context of AAT patients/participants who are likely to enjoy animals. In other words, a person who dislikes animals will refuse intervention from the beginning.

The results of this study suggested that the RCTs conducted have been of relatively low quality. Only two RCTs were evaluated as "good description (80—100%)".[15,22] AAT with dolphins is an effective treatment for mild to moderate depression, and is based on a holistic approach through interaction with animals in nature.[15] AAT also plays an important role in enhancing the benefits of conventional therapy in psychiatric rehabilitation.[22] Furthermore, AAT may have positive effects on schizophrenia and/or serious mental disorders. We assume that the direct effects of AAT are generally improvement of mental health, elimination of the sense of isolation, and an improvement in QoL.

Although further accumulation of RCT data is necessary, AAT may be effective treatment for the following diseases and symptoms: cancer and/or advanced life-limiting illnesses that affect mental state and QoL, impaired circulatory function with mechanical assistance, autistic spectrum disorders involving communicative skills, and self-reported outcomes for hospitalized patients and other patients with various clinical conditions.

Future research agenda to build evidence
Table 5 shows the future research agenda for studies of the cure effect by AAT. Researchers should use the appropriate checklists for research design and intervention methods, which would lead to improvement in the quality of the study, and would contribute to the accumulation of evidence. Researchers should also present not only efficacy data, but also a description of any adverse events or harmful phenomena and the reasons for withdrawals and non-participation. Many studies in this review did not describe these factors.

As a gradual increase of intervention is necessary in cure and rehabilitation programs, it is easy to assign settings like "Stage" for the intervention, such as first stage and second stage. Therefore, we also expect to understand the results and detailed descriptions of "pragmatic trials"[30] as well as "explanatory trials" for the treatment effect by AAT.

Bowen et al.[31] suggested that public health is moving toward the goal of implementing evidence based intervention. But the feasibility of possible interventions, and whether comprehensive and multilevel evaluations are needed to justify them, must be determined. It is at least necessary to show the cost of such interventions. Introduction of an interventional method must be based on its cost—benefit, cost—effectiveness, and cost—utility.

In addition, AAT as an intervention is unique and completely different than pharmacological or traditional rehabilitation methods. Therefore, it may be necessary

Table 5 Overall evidence and future research agenda to build evidence.

Overall evidence in the present	Research agenda
After having premised study environment limited to the people who liked animals very much, 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.	1. Satisfactory description and methodology including the CONSORT 2010 and the CONSORT for nonpharmacological trials 2. Description of the reason of participants refused (non-participation) 3. Description of adverse effects (e.g., allergy, infection, bit, and fear) and withdrawals 4. Description of intervention dose (if pragmatic intervention) 5. Description of cost 6. Development of the original check-list for AAT

to add some original items like herbal intervention,[32] acupancture,[33] traditional Chinese medicine[34] and balneotherapy[35] to the CONSORT 2010 checklist as alternative and/or complementary medicines.

Strength and limitations

This review had several strengths: (1) the methods and implementation registered high on the PROSPERO database; (2) it was a comprehensive search strategy across multiple databases with no data restrictions; (3) there were high agreement levels for quality assessment of articles; and (4) it involved detailed data extraction to allow for collecting all articles' content into a recommended structured abstract. The conduct and reporting of this review also aligned with the PRISMA statement[36] for transparent reporting of SRs and meta-analyses.

This review had several limitations that should be acknowledged. Selection criteria were common across studies, as described above; however, bias remained due to differences in eligibility for participation in each study. Publication bias was a factor. Although there was no linguistic restriction in the eligibility criteria, we searched studies with only English and Japanese key words. In addition, this review reported on a relatively small and heterogeneous sample of studies. Moreover, we could not follow standard procedures for estimating the effects of moderating variables.

Conclusion

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.

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

Contributors

TH, JK, SP, SO, HO, SH, HP, TO, and TA conceived the study and take responsibility for the summary of included studies and data extraction. KT and YM are the guarantors. HK and SO designed the study. HO, SP, TH and HK assessed the quality of articles. All authors critically described the manuscript for important intellectual content.

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Data sharing

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