

Review

Professional ethics in complementary and alternative medicines in management of Parkinson's disease

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Abstract. The practice of complementary and alternative medicine (CAM) is not, at present, considered an integral part of conventional medicine. As the popularity of CAM grows and access to information about CAM increases through the media and internet where CAMs are often promoted, patients are at risk of exposure unvalidated information. Therefore, there is a need for physicians to examine objectively the efficacy and safety of CAM, compare it with current medications, and become actively involved in the CAM treatment with patients. In accordance with these needs, this manuscript reviews the utility, scientific evidence, safety and cost-effectiveness of CAM in the treatment of Parkinson's disease (PD). We also address the ethical issues of CAM practices.

Keywords: Parkinson's disease, complementary and alternative medicines, complementary medicines, traditional medicine, acupuncture, herbal medicine, review

INTRODUCTION

Since Parkinson's disease (PD) is a progressive neurodegenerative disease, patients continue to experience a decline in function and capacity for daily activities despite optimal medical or surgical management [1]. It is, therefore, understandable that patients often seek other resources such as complementary and alternative medicine (CAM), hoping that such treatments might bring symptomatic relief or stop the progression of diseases they have been told modern medicine cannot cure.

However, many experts and critics have raised concerns that the popularity of CAM is growing without scientific support or evidence for efficacy, as discussed by Ernst [2]. He pointed out that the ethical principles which apply to medicine in general should apply to CAM, but at this stage CAM is largely unregulated. He was particularly concerned about the use of ineffective procedures, publication of false health claims, misuse of the title 'Doctor' by non-medically trained clinicians, the failure to obtain informed consent, the failure to monitor and report adverse effects, the nondisclosure of conflicts of interest, and the fabrication of research data [2]. In spite of all these concerns, patients with chronic nervous system diseases, including PD, are willing to receive experimental treatments, even at the risk

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of experiencing adverse events [3, 4], as evidenced in our Korean nationwide survey of PD patients and caregivers. In our survey of patient knowledge and attitudes towards experimental treatments, more than 50% of patients responded they did not possess correct information regarding safety and efficacy of stem cell transplantation or bee venom acupuncture [3]. More disturbing was the finding that 55.3% and 42% of patients with PD answered that they were interested in receiving stem cell transplantation or bee venom acupuncture respectively, despite a lack of evidence of the safety and efficacy of these experimental treatments [3]. Because of a desperate desire for a cure, patients choose CAM based on limited information from uncertain sources rather than scientific evidence despite the possibility of being ineffective or even harmful, and a waste of time and cost. Information sources for CAM are rarely objective and in the case of PD mainly from friends [5, 6], a relative or a neighbor [5–7], or patients themselves [8]. Only 11–20% of patients who used CAM received their referral from a healthcare professional or an oriental medicine physician [5–8].

Another disturbing point about CAM usage is that patients are reluctant to inform their treating physicians, who may be unaware of what medications are being taken and therefore cannot provide help for the actual conditions [9]. Among PD CAM users, 16% and 57.1% informed their physicians of their use of CAM in Singapore and Argentina, respectively [6, 7]. More than half did not consult their treating physician before starting CAM in USA [5]. Patients usually do not inform their physicians about CAM because they assume the physician does not need to know, or they presuppose a negative reaction from the physician [10]. There is, therefore, a risk of harm as they are not properly advised by informed medical professionals.

Hence, there is a need for physicians to assess objectively the efficacy and safety of CAM scientifically, compare it with the evidence for current medications, and become actively involved in the CAM treatment with patients. In accordance with these needs, we review the utility, scientific evidence, safety and cost-effectiveness of CAM in PD and address the ethics of CAM practices.

DEFINITION OF CAM

The National Center for Complementary and Alternative Medicine (NCCAM) defines CAM practices as those not, at present, considered an integral

part of conventional medicine [11]. The words “complementary” generally refers to using a non-mainstream approach together with conventional medicine, while the word “alternative” refers to a non-mainstream approach in place of conventional medicine [12]. The NCCAM has grouped complementary treatments into three main domains: 1) Natural products including a variety of products such as herbs, vitamins, and minerals, and probiotics; 2) mind and body practices including a large and diverse group of procedures or techniques administered or taught by a trained practitioner or teacher – for example, acupuncture, massage, meditation, movement therapies, relaxation techniques, spinal manipulation such as chiropractic and osteopathic manipulations, tai chi, qi gong, yoga, healing touch, and hypnotherapy; 3) other complementary health approaches which may not neatly fit into either natural products or mind and body practices – for example, the practices of traditional healers, Ayurvedic medicine, traditional Chinese medicine, homeopathy, and naturopathy [12].

EPIDEMIOLOGY OF CAM

CAM use is common among PD patients across the globe. In Asia, frequency of CAM use is 61% and 76% in Singapore and in Korea, respectively [6, 8]. However, it is also high in western countries ranging from 34 to 54% [5, 7, 13, 14]. Although a diverse spectrum of CAM is used for PD, acupuncture is the intervention most often used worldwide [15]. Other commonly used CAMs included massage, herbs, and vitamins/health supplements. Cultural background appears closely related to selection of CAM type [15]. Natural products such as vitamins and herbs were the most commonly used CAM for PD in the US [5], while mind and body practices such as acupuncture, yoga, and massage were common in Sweden [13], Argentina [7], and the UK [14]. In Asian countries, traditional or oriental medicine was the most common CAM [6, 8].

Although the main reason for trying CAM in patients with PD was to improve PD symptoms, a number of patients chose CAMs for other reasons such as “own belief in the treatment” [13], “use as a tonic” [14], and even for no specific reasons [8]. Other reasons included enhancement of the effects of prescription medications [6], and the management of non-motor symptoms, such as fatigue [8], pain [8, 14], and constipation [8].

Socio-demographic factors correlated with CAM use were higher income [5], rural location [8], perceived poor health [13], female gender [7], and younger age [14]. Some studies showed CAM users had a higher educational level than CAM non-users [5, 13]. Kim, et al. found that patients with lower educational level tended to favor traditional oriental medicine and those with a higher educational level tended to favor traditional food and massage therapies, suggesting that specific modalities of CAM may vary depending on educational background [8]. Certain disease-specific factors, such as younger age at onset of PD [5, 14], higher levodopa dose [8], severity of symptoms [6], and longer duration of PD [8] were related to CAM use. However, none of the socio-demographic factors or disease-specific factors have been consistently associated with the use of CAMs in other studies.

SELF-REPORTED EFFICACY OF CAM

Three studies evaluated self-reported efficacy using a structured or semi-structured questionnaire exploring the usage of CAM [6, 8, 13]. Response rates varied from 81% to 100% [6, 8, 13]. Forty percent of CAM users in Singapore subjectively reported some degree of improvement, 58% reported no improvement and 2% reported a worsening of their parkinsonian symptoms [6]. Although 41.6% (37/89) of CAM users in Korea reported an improvement in their PD symptoms, the majority (83.8%) reported only a mild beneficial effect and 9.6% (9/94) experienced adverse effects from CAM. Nonetheless, 57.4% of CAM users answered that they planned to continue using CAM [8]. In Sweden, self-reported efficacy differed depending on type of CAM [13]. For acupuncture, 50% found no improvement while 50% reported some improvement. For herbal medicines and other drugs, one third reported good improvement, one third some improvement and the remaining third no effect. However, the majority reported no effect for other CAM alternatives [13].

SCIENTIFIC EVIDENCE REGARDING EFFECTIVENESS OF ACUPUNCTURE FOR PD

Experimental studies

During the last decade, several experimental studies suggested that acupuncture may have

neuroprotective effects [16–30] as well as symptomatic benefits [19, 24–29, 31–39] in PD animal models. The suggested neuroprotective mechanisms include reduction of oxidative stress [30, 33, 37], up-regulation of neurotrophic factors [17, 35, 39], modulation of neuronal activity in basal ganglia circuits [31, 32, 35], attenuation of microglial activation [18, 21, 23], and modulation of apoptosis [22, 29, 33], and neuroinflammation [18, 21, 23, 33]. However, the precise mechanisms of the putative neuroprotective and therapeutic effects of acupuncture are still unclear. There are no studies evaluating the long-lasting effect of acupuncture following cessation of treatment. Thus, whether the neuroprotective effect of acupuncture is transient is not known.

In acupuncture, disease is explained by an imbalance in the flow of life energy “Qi” through the meridian system, which is accessible at various points. Thus stimulating acupoints is believed to restore body homeostasis. If some points are considered more therapeutically valuable than others, selection of acupoints may be critical. Nevertheless, there was no consensus of animal acupoints among the experimental studies reviewed. The acupoints used in Korean and China were far different [16–22, 24, 26, 28–32, 34, 35, 37, 38, 40]. Moreover, selection of acupoints differed depending on study groups within China. To demonstrate the distinctive and beneficial effects of a specific acupoint, nonacupoint acupuncture as well as placebo acupuncture is needed as a control intervention group. However, nonacupoint acupuncture has not been applied in the majority of reported studies [17, 18, 22, 26–32, 35, 38, 40].

The parameters and treatment regimens of acupuncture are said to be related to its therapeutic effect. However, needle type, depth of insertion, and needle retention time were not consistent across trials. Frequency, duration, and number of treatment sessions were also highly variable. Several studies did not even report some of those parameters. There were also regional differences in the selection of acupuncture type. Electroacupuncture was preferred over needle acupuncture in China [17–19, 30–32, 35, 36, 38, 39], while needle acupuncture [20, 21, 24–26, 29, 34, 40] and venom acupuncture [22, 23] were preferred in Korea.

Randomized Clinical Trials (RCTs)

The effectiveness of acupuncture in PD has been tested in many controlled clinical trials but few

systematic reviews of these studies are available. Most of the published RCTs assessed the effect of acupuncture as monotherapy or as adjunctive therapy to conventional drugs and suggested that acupuncture had a higher efficacy than conventional drugs or no treatment on the Webster rating scale scores, Unified Parkinson's Disease Rating Scale (UPDRS), or Motor Dysfunction Rating Scale for PD. However, there are a limited number of clinical trials using placebo acupuncture as a control intervention. When compared with nonacupoint acupuncture, both acupuncture [41, 42] and electroacupuncture [43] failed to show favorable effects on UPDRS. Meta-analysis of these data also showed no significant effect of acupuncture [44], suggesting the possibility of a placebo response to acupuncture.

To date, four systematic reviews regarding efficacy of acupuncture in PD have been published [44–47]. The common conclusion of these reviews is that evidence for efficacy of acupuncture in PD was not convincing because of the poor quality of the trials. Lam, et al. searched acupuncture studies for PD in 13 databases, and found that only 10 of 784 studies met the criteria for RCTs [45]. All 10 RCTs showed serious problems in methodology and reporting, although 9 studies claimed a statistically significant positive effect from acupuncture compared to controls. In the review by Lee, et al., 11 of the 103 studies reached a level of RCTs, and these were subsequently evaluated [44]. Seven of 11 RCTs included in the analysis were rated as being of low methodological quality. All the low-quality RCTs generated positive results compared with 33% of high quality trials. It is well known that trials with less methodological rigor are more likely to exaggerate treatment effect than rigorous studies [48, 49]. Evidence-based medicine reviews by the Movement Disorder Society also concluded there is insufficient evidence to support acupuncture as symptomatic monotherapy, adjunct therapy to levodopa, in the prevention of clinical progression and motor complications, or as treatment of motor complications [50].

Besides inadequate control of placebo effects and poor methodology, heterogeneity in acupoints and acupuncture method (type, parameter, and schedule) has limited the reliability of clinical studies on acupuncture. As in experimental studies, there was no consensus in acupoints between investigators in clinical trials. The discrepancy in acupoint locations results in difficulty in interpreting and comparing studies reported in the literature [51]. As five or more acupoints were selected at a time in most

of the clinical trials [44, 47], it could not be determined which acupoint was indeed effective. Only a few acupoints were used repeatedly, while most of acupoints were used only in 1 or 2 trials [45, 47]. Moreover, the efficacy of acupoints applied in clinical trials was seldom investigated in experimental studies [47]. Acupuncture parameters such as stimulation frequency and duration, retention time, and treatment sessions were variable between trials.

SCIENTIFIC EVIDENCE REGARDING EFFECTIVENESS OF AYURVEDA IN THE CLINICAL TRIALS FOR PD

There are only four clinical trials using Ayurvedic medicines in PD and no systematic review or meta-analysis. Three were open clinical trials [52–54] and one was a pilot study with a randomized, controlled, double blind, crossover design [55]. Ayurvedic medicines other than *Mucuna pruriens* were seldom evaluated in clinical trials. Although open clinical trials suggested some beneficial effect of Ayurvedic treatment, there was no adequate control or placebo group [52, 53]. Thus potential placebo effects cannot be excluded. In the pilot study, patients on *Mucuna pruriens* had longer on-time & higher peak levodopa concentrations, compared with an equivalent dose of L-dopa, however, no significant difference was observed in the UPDRS motor score and dyskinesia score [55]. Each of the tested drugs was administered just once and sample size of this study was small.

Although the value of observation studies cannot be ignored, controlled clinical trials provide higher levels of evidence [56] and are the gold standard for measuring the efficacy of all medical interventions, including CAM methods [57]. Unfortunately, the number of clinical trials of Ayurvedic medicines in PD is insufficient and the design, methodology and quality of clinical trials lack the rigor to reach any recommendation.

SCIENTIFIC EVIDENCE REGARDING EFFECTIVENESS OF HERBAL MEDICINE FOR PD IN CLINICAL TRIALS

To our knowledge, there are only three systematic reviews or meta-analysis analyzing RCTs for efficacy of herbal medicines in PD [58–60], although numerous clinical trials have reported beneficial effects of Chinese herbal medicine in PD. In a systematic

review by Chung, et al., 9 RCTs were included, each testing a different herbal medicine with varying compositions [58]. Of 4 studies examining herbal medicine as monotherapy, 3 including one testing *Mucuna pruriens*, reported similar or superior efficacy of herbal medicine compared to conventional drugs on the Webster rating scale score, UPDRS motor score, Abnormal Involuntary Movement Scale, or Goetz scale. Herbal medicine as an adjunct therapy in 5 studies also yielded a better outcome compared to the sole use of herbal medicine or conventional drugs on Webster rating scale score or UPDRS scores. However, the sample size in individual trials was relatively small suggesting the possibility of exaggeration of the efficacy of herbal medicine. Moreover, all trials except one used unvalidated diagnostic criteria. Only one trial with cross over design had placebo control and failed to show therapeutic effect of herbal medicine on dyskinesia, overall UPDRS, and PDQ-39. Seven out of nine trials were conducted in China, and of the latter, 6 had major methodological design flaws.

A meta-analysis by Wang, et al. included 19 studies, which assessed clinical efficacy of Chinese herbal medicine for PD [59]. Compared with conventional treatment, herbal medicine as an adjunctive therapy improved UPDRS I, II, III, IV, and total scores. Although the 16 herbs were used more than 3 times in the 19 trials, herbal medicine differed in composition, dosage preparation, and methods or manufacturing standards. Therefore, it is difficult to assess the effect of a particular herbal medicine. Based on the funnel plot, there exists a publication bias for UPDRS III scores in the 12 trials and for UPDRS IV scores in the 7 trials with mainly positive results, and only 4 trials had placebo control. Regarding diagnostic criteria for PD, four trials used the UK brain bank diagnostic criteria, while the others used the Chinese National Diagnosis Standard. Only 8 trials provided sufficient information for randomization, 4 for blinding, and 3 for dropout rates.

Kim, et al. reviewed 64 studies among 2432 relevant publications from 15 electronic databases to evaluate the evidence of herbal medicine for PD [60]. In these 64 studies, 59 herbal preparations were used, and of these, 5 herbal medicines were used several times. Herbal medicines were composed of 3 to 20 herbs, in all studies except two. Many studies compared combination therapy with single active drugs. Combination therapy showed an improvement in PD related outcomes and a decrease in the dose of antiparkinsonian drugs. However, the funnel plots

appeared asymmetric, which might have originated from publication bias or poor methodological qualities of the included studies. Out of 64 studies, only 14 were placebo controlled. When compared with placebo, specific effects were not observed in favor of herbal medicines. Direct comparison with conventional drugs also suggested that there was no evidence of better effect for herbal medicines. When risk of bias was assessed according to the criteria of Cochrane collaboration in 6 domains including random sequence generation, allocation concealment, blinding of participants, incomplete outcome data, selective reporting and other bias, none of the studies had low risk of bias in all 6 domains.

SAFETY OF CAM

CAM-researchers often failed to mention the adverse effects that may have occurred during the clinical trials [44–47, 58–60], and information about safety and adverse drug reactions in CAM is not readily available [57]. Consequently, some people may be lead to believe that CAM is safe while western medicine is toxic. Like the conventional treatments, CAMs are not free of risk. For example, *Ashwagandha* can cause thyrotoxicosis [61], and Chinese herbs extracts containing Aristolochic acid have been reported to cause a rapidly progressive interstitial nephritis leading to end-stage renal disease [62]. Herbal medicine related hepatotoxicity is not uncommon [63–65]. Weight reducing herbal medicines have been reported to cause hepatitis, hepatic failure, and even death [63, 65]. Some commonly used herbs have been associated with allergic and toxic reactions [63]. Saper, et al. reported that one-fifth of Ayurvedic medicine produced in South Asia and available in Boston South Asian grocery stores, or purchased via the internet, contained potentially harmful levels of lead, mercury, and/or arsenic [66, 67]. Indeed, since 1978, more than 80 cases of lead poisoning associated with Ayurvedic medicine use have been reported worldwide [66]. Adverse effects are not only limited to Ayurvedic or Chinese herbal medicine. Live bee acupuncture therapy, can cause acute and chronic inflammatory reactions, and the venom may act as an allergen in some patients causing a severe immunological response such as anaphylaxis [68]. Aromatherapy and homeotherapy also can cause serious adverse events such as dermatitis, pulmonary edema, seizures, allergic reaction or ingestion of toxic substances [69, 70].

The risk of drug interactions also applies to CAM and can lead to serious consequences if patients do not inform physicians of the concomitant use of CAM and conventional medicines. Herbal compositions are generally complex and heterogeneous. Although the combination of several herbal medicines may provide some synergistic effects, using multiple herbs can increase the risk of side effects and unwanted herb-herb or drug-herb interactions. Dasgupta suggested that herbal supplements can affect concentrations of therapeutic drugs by direct interference with the measurement methodology or indirectly by altering the pharmacokinetics of co-administered drugs [71]. The ways in which CAMs interact with conventional medicines and disease status remain unsolved.

Another negative consequence of CAM is that patients may miss the chance or optimal time to receive proven effective therapy as has occurred in several high profile cases [72, 73].

CAM non-medical practitioners should be able to recognize serious and acute cases by symptoms in order to refer those patients to their treating physician, while at the same time it is of paramount importance that the patients inform the latter of their use of CAMs [57]. In Korea, it is not rare for a patient with an acute stroke to visit an oriental medicine clinic. If a patient is not referred to the hospital within the window of opportunity, he or she might miss the benefit of fibrinolytic therapy, resulting in serious sequelae. Therefore education about basic medical standards should be mandatory during CAM teaching courses.

COST OF CAM

The cost of CAM is not cheap. With the increasing use of CAM worldwide, there is a tendency for the cost of CAM to rise. According to a recent report by the Korean Health Insurance Review & Assessment Service, the amount spent on traditional Korean medical treatment continues to rise at the rate of 7.7%/year [74]. At this point, we need a cost comparison of CAM versus modern PD therapy.

Kim, et al. showed that the mean cost of CAM paid by patients (out-of-pocket expense) was 102.3 US Dollars (USD) per month, whereas the cost of medical treatment for PD paid by patients averaged 72.8 USD per month [4]. Another Korean study reported that the cost for CAM was 12.4 times higher than that of standard therapy, although CAM showed only partial relief of PD symptoms in 20% of CAM users [75]. In Singapore, the average duration of use for each

CAM was 31 months with an average cost of 43.53 USD/person/type of CAM/month [6]. In Sweden, 20% of CAM users reported spending the equivalent of 50€ on CAM during the previous 6 months [13].

ETHICAL CONSIDERATIONS

Reporting adverse events is important to protect patients from potential risks and to prepare safety measures [76]. Therefore, a patient's condition should be monitored appropriately during treatment with systematic documentation so that reliable data on pharmaco-epidemiology and pharmaco-vigilance for safety and adverse drug reactions can be made. Currently, CAM is not regulated as rigorously as conventional medicine in terms of standardization and quality specification, and pre-marketing research and post-marketing risk management are still in an early stage in CAM, although a modest beginning has been made [56, 64, 65, 77, 78].

From an ethical point of view, all relevant information about treatment options should be given to patients. Informed consent is dependent on the patient's competence to understand treatments and their consequences, and also on the ability of the health care provider to inform the patient appropriately [79]. Although healthcare providers should know about the safety of the remedies they prescribe, there is a limitation of currently available information concerning the safety of CAM. How should consent be determined where there is insufficient information about the risks?

All patients have the right to choose the treatment, and their decision has to be respected. However, not all options that patients prefer and choose are necessarily wise. Sometimes a patient might choose a CAM therapy according to spiritual beliefs, even if there is evidence that such therapy is not beneficial [79, 80]. In such situations, patient autonomy may conflict with the ethical responsibility of the health care provider. However, when principle of beneficence and non-maleficence is considered, approval or cooperation for using an unproven therapy and merely waiting to see what happens could also be considered unethical [2]. We also should consider whether expenditure on uncertain or ineffective treatments, even if harmless, is justifiable or ethical.

Another consideration is whether integrating CAM into a health care system is ethical. In Korea, some kinds of CAMs are part of the public health care system and costs are covered by a national health insurance system. In many countries, CAM services

are not part of the public health care system, and must be paid for by either the patients themselves or by private health insurance. Assuming that CAM does more good than harm, this situation is not equitable because the unequal distribution of CAM within the population violates the fundamental ethical principle of justice. If efficacy and safety of CAM are uncertain, the integration of CAM into a health care system may be in conflict with the principles of beneficence and non-maleficence [81].

CONCLUSION

The available evidence for efficacy of CAM is insufficient and little is known about safety, despite widespread use of CAM practices among patients with PD. With increasing access to information about CAM through the media and internet where CAMs are often promoted, patients are more likely to be exposed to unvalidated information and potential risks from unproven treatments. Therefore physicians should educate themselves about evidence-based CAM treatments and provide responsible information about CAM to patients, thus helping patients to make proper decisions regarding the use of CAM.

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