Complementary Medicine Research

Journal Club

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Quo Vadis TCM? - From the Long Road of Traditional Chinese Medicine to Scientific Acknowledgement

The present Journal Club departs somewhat from the previous template, which normally calls for commentary on at least three interesting publications by different authors. This practice is good in principle and has proven to be effective in terms of diversity of opinion. Nevertheless, I take the liberty to make an exception in the case of the here so complex topic „Traditional Chinese Medicine (TCM)" and to discuss the publication situation of TCM in its problematic as editor responsible for the Journal Club by myself and without co-authors.

This is being prompted by the statement of the EASAC (European Science Advisory Council) and FEAM (Federation of European Academies of Medicine) on the topic of „Traditional Chinese Medicine" written in 2019 [1,2]. The EU scientific academies raise strong concerns about the inclusion of an additional chapter for TCM by the WHO (World Health Organization) as part of the revision of the ICD-11 classification (International Statistical Classification of Diseases and Related Health Problems). The concern would be that a false impression could arise for politicians, health insurers, doctors and patients that TCM is adequate and scientifically equivalent part of conventional medicine and that the inclusion in the ICD-11 could possibly also lead to the reimbursement of treatment costs by the statutory sickness funds [1].

With the future use of the ICD-11 from January 1, 2022, the additional chapter 26 offers TCM-interested physicians the use of 150 functional disorders and 196 symptoms, finding and behaviour patterns for TCM diagnosis coding in English. The adoption of the chapter in the respective countries or their translation into the national language is voluntary and remains to be seen. Overall, the necessary evaluation process and a possible introduction of the ICD-11 here in Germany will take several years anyway. It is not yet clear whether a comprehensive consideration of the differentiation of findings and symptom patterns in TCM diagnostics will lead to significantly better results in treatment. So far, the written recording of TCM diagnoses, even in the usual standard medical documentation, is still not very widespread in China itself (and probably not elsewhere either). This will therefore lead to a considerable additional effort in routine documentation in TCM medical practices worldwide and will not meet with an unbiased acceptance everywhere. However, a phenomenologically descriptive finding of diagnosis, as is typical for many complementary healing methods, can significantly improve the application practice through more uniform nomenclatures and their education. Standardization of items also supports government regulation, clinical trial implementation, and outcome-based health services research. This is particularly the case because there is currently no sufficient EU-wide research infrastructure for complementary medicine in the individual member states and their universities.

But why this vehement rejection by the EU science advisors is happening in this undifferentiated and sweeping way is not substantiated and goal-oriented. Especially not when - with good reason - more scientific reappraisal is called for. However, the statement does not only refer its criticism to the planned integration of a TCM-specific nomenclature into the ICD-11 framework, but also includes other areas of TCM. For instance, the facilitated registration practice for traditional her-

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bal medicinal products with the European Medicines Agency, which was enacted in 2004 with Directive 2004/24/EC, is again generally criticised as no longer up to date. The current practice allows manufacturers of traditional herbal medicinal products „only" to submit evidence of 30 years of use (of which at least 15 years within the EU) and bibliographic as well as expert-based evidence on these products [3]. EASAC had already criticised this procedure in 2017 for the registration of homeopathic products and questioned the whole of homeopathy in its statement. Furthermore, the controversial state of the evidence on acupuncture was pointed out [4].

In principle, this criticism of content is legitimate. It would be more advantageous if these bodies also had experts who could draw on their own scientific and practical competence in this field. Basically, this would make it possible to provide the EU with more objective advice on complementary medicine. Since Traditional Chinese Medicine is one of the most common complementary therapies worldwide and numerous international research activities are striving for modernisation and clinical evidence, a brief insight into clinical research and its methodological challenges will be given here on the basis of exemplary publications.

Quantity and Quality of Clinical Trial Activities in Traditional Chinese Medicine

In order to get a good overview of clinical research activities in the field of TCM, it is worthwhile to consult the clinical trials registry database (International Clinical Trials Registry Platform - ICTRP) set up by the World Health Organisation (WHO). Zhang Xuan's working group analysed the TCM clinical trials registered in the ICTRP in 2018 and published the results in the following paper [5]:

Zhang X, Tian R, Yang Z, Zhao C, Yao L, Lau C, Wu T, Shang H, Zhang X, Lu A, Bian Z. Quality assessment of clinical trial registration with traditional Chinese medicine in WHO registries. BMJ Open. 2019 Feb 19;9(2):e025218. doi: 10.1136/bmjopen-2018-025218.

The working group examined the study quality of all TCM clinical trials registered with the WHO ICTRP platform between 1999 and 2017. The reporting quality of the studies found was analysed according to at least 20 ICTRP criteria relating to general study quality and according to 3 TCM-specific quality criteria. Zhang X. inventoried a total of 4326 studies; of these, 3339 studies were included in the final analysis. Studies that did not clearly relate to TCM components such as acupuncture, moxibustion, TCM medicines, QiGong and/or to TCM theories were excluded. The majority of the studies examined on the 15 international registry databases linked to the ICTRP platform were on the Chinese (Chinese Clinical Trial Registry) and American registry database (Clinical Trials gov.). More than half of all studies found and analysed were registered within the years 2015-2017, reflecting the enormous dynamic of research activity. Overall, 61% of the studies were registered prospectively and 39% retrospectively. Counting the studies according to the respective countries in which the patients were recruited, 1918 studies, or 57.4%, were conducted in the People's Republic of China and 1421 studies (42.6%) were performed in other international countries. Germany contributed 2.1% (70) of the clinical trials. Among the pure intervention studies (88.5%, 2955/3339), acupuncture was the most frequently investigated TCM intervention with 50.2%, followed by Chinese medicines with 30.1%. Primary sponsors of the studies were hospitals for more than half and universities for one third. Industry and government together funded 3.1% of the registered studies. However, the share of government funding is likely to be significantly higher from Chinese studies, as hospitals in China use government funds and this is part of the allocation truth. Unlike Western governments, TCM in the People's Republic of China is supported by the state through its own ministry.

Of the analysed clinical trials, 1473 (44.1%) had already been completed, 1166 (34.9%) were in the recruitment phase and 50 had been stopped. The study design was randomised in 84% of all trials, blinded in 29.2% and multi-centre in 11.1%. In more than half (55.6%) of all studies, the patient cohort was smaller than 100 persons. With regard to the quality criteria of the ICTRP (International Standards for Clinical Trial Registries), the majori-

Table 1. Recommendations for registration, conducting and reporting of clinical randomised trials and reviews in the field of TCM (Melchart)

Year	Quality Measures introduced in China	References
1997	CONSORT statement (JAMA Chinese Edition)	Begg C [6]
2003	CONSORT and STRICTA (introduced in China)	Liu SM [7]
2010	Revised STRICTA (Standards for Reporting Interventions in Clinical Trials of Acupuncture): Extending the CONSORT statement	MacPherson H [8]
2013	CONSORT (Consolidated Standards of Reporting Trials): Extension for Moxibustion	Cheng CW [9]
2017	CONSORT – Extension for Chinese Herbal Medicines Formulas	Cheng CW [10]
2018	SPIRIT (Standard Protocol items for clinical trials with traditional Chinese medicine): Extension for TCM	Dai L [11]
2019	PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses): Extension for Acupuncture	Wang X [12]
2015	CONSORT – Extension for reporting N-of-1 trials (CENT) 2015	Shamseer L [13]
2019	CENT for TCM 2019	Li J [14]
2020	PRISMA – Extension for Moxibustion	Zhang X [15]
2020	PRISMA – Extension for Chinese Herbal Medicines	Zhang X [16]
2020	WHO Trial Registration Data Set (TRDS) – Extension for traditional Chinese medicine	Zhang X [17, 18]

ty of the studies had shortcomings such as retrospective registration, lack of linking of publications to the registration platform and inadequate information on formal study criteria as well as the lack of TCM-specific indicators (e.g. exact intervention description, TCM diagnoses).

Nevertheless, the high number of clinical studies with randomisation and the likewise high international participation of scientific working groups in the topic of TCM is surprising. Since the scientific movement in TCM research is not likely to have slowed down in the last three years, a further increase in the number of studies can be assumed. Certainly, these increased registration activities and high numbers of published study-protocols must also be observed critically. On the one hand, it must be checked whether the number of study projects have actually been implemented and whether the clinical results have been published or the expected study dropouts have been communicated to the registries. However, these audits do not apply to clinical TCM research alone, but also to all other medical study areas. Nevertheless, TCM and many other complementary medicine fields have a quality problem in the conducting of clinical trials, which cannot be compensated by mere quantity.

If we look at the formal validity of TCM clinical studies, the conclusions of almost all clinical study authors surprise us again and again that the analysed studies show considerable BIAS problems and that methodologically better studies would be necessary in the future in order to find conclusive evidence. Before we address this problem using the example of acupuncture and chronic back pain, we will first reflect on important efforts made by professional societies and scientific working groups to improve the methodological quality of clinical studies in the field of TCM over the last 25 years. Table 1 provides a brief overview. All major methodological recommendations for enhancing the reporting quality of controlled randomised trials, such as the CONSORT checklist [6,7], have been adapted to the different TCM methods such as acupuncture (STRICTA), moxibustion and the Chinese medicines (Chinese Herbal Medicine Formulas) [8-16]. There are also current recommendations for the registration of TCM studies with the WHO-ICTRP on how TCM studies can be better described in terms of their TCM-specific information, in order to achieve more quality and transparency [17]. For example, the current 2020 checklist for registration with the WHO TRDS platform contains a total of 11 items for TCM studies, which also take into account „TCM patterns“ (e.g. qi deficiency pattern, qi stagnation pattern) and detailed descriptions of TCM interventions for the various forms of acupuncture, moxibustion and traditional Chinese medicines (decoctions, pills, powders, granules, capsules, etc.) [17,18].

There is thus a high commitment to methodological quality improvement of TCM clinical trials in terms of study registration, conduct, publication and their statistical evaluation. Nevertheless, compliance and adherence to these formal quality requirements by the study trialists appears to be still not high enough. This is shown in particular by publications from Ma B. et al. 2016 and Long Y. et al. 2020, which examined the study quality of Chinese and other international randomised clinical trials (RCTs) on acupuncture and moxibustion over the past decades [19,20]. Ma Bin examined 1978 RCT studies published in Chinese medical journals between 1997 and 2012 and compared the quality of the studies in the periods before and after the introduction of CONSORT and STRICTA in China with regard to the fulfilment of the required items of the methodological quality domains [19]. Although there were improvements in principle between 1997 and 2012 in items such as randomisation (1.4% to 26.3%), significant problems, such as the allocation of patients to the respective study groups without bias or pro-

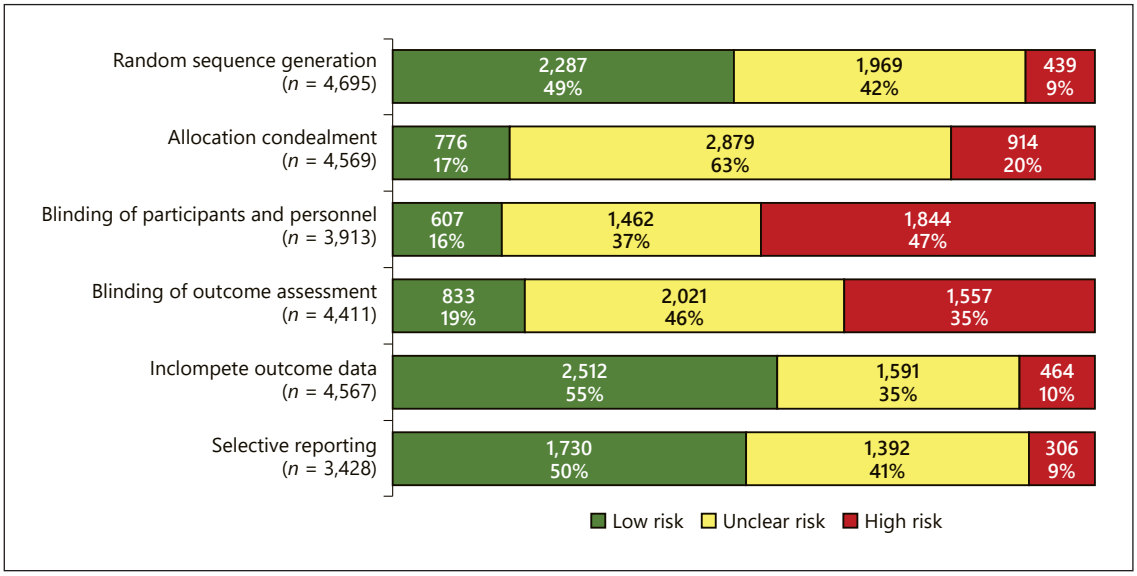

Figure 1: Risk of Bias (RoB) for the individual quality domains of GRADE from Long Y et al. PLoS One 2020

blems with blinding of therapy and persons remained (0% vs. 4.9% and 0% vs. 9.1%, respectively). The same quality shortcomings were also found in the 2020 paper by Long Youlin, who examined 368 systematic reviews of a total of 4715 RCTs with acupuncture and moxibustion from 1974 to 2017 [20]:

Long Y, Chen R, Guo Q, Luo S, Huang J, Du L. Do acupuncture trials have lower risk of bias over the last five decades? A methodological study of 4 715 randomized controlled trials. PLoS One. 2020 Jun 10;15(6):e0234491. doi: 10.1371/journal.pone.0234491.

The analysis also included international studies from the PubMed and Embase databases. The high „risk of bias (ROB)" values often led to the downgrading of recommendation levels according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system. It is precisely the loss of scores in the quality domains „Blinding of participants and personnel", „Blinding of outcome assessment" and „Allocation concealment" that lead to low evidence recommendations (see figure 1).

If we only consider the sheer number of 4715 RCTs in the field of acupuncture and moxibustion, we are shocked by the high consumption of human and financial resources on the one hand, but we also have to acknowledge the high scientific commitment shown on the other. But why is there still no methodological consensus for a solution? In principle, allocation problems could be eliminated by involving accompanying central and independent study centres. Clearly more difficult is to find solutions for suitable blinding procedures for manual treatment techniques such as acupuncture and moxibustion. This is obviously because the acupuncturist needs to know where he or she is puncturing, and patients can usually tell whether an acupuncture needle has been inserted or not. Even using sham needles and non-penetrating placebo needles at the same time for a control treatment does not solve the problem. A „sham-acupuncture" i.e. the pricking of an area of the body that does not have acupuncture points is not an „inert" placebo and therefore not an ideal study control. Furthermore, there are also major differences between „sham" and „verum" acupuncture depending on, among other things, needle manipulation, duration of treatment, location of pain and group size.

The work by Li C et al. 2020, reviewing 77 RCT`s of acupuncture treatments for chronic shoulder, neck, knee and back pain, shows that the differences on a 0-100 point NRS scale measuring pain intensity (baseline 60 points) between sham, verum and conventional standard treatment are a mean pain reduction of 22.6 vs. 34.9 vs. 15.8 points. When only considering chronic back pain, verum acupuncture is shown to be significantly less effective than the other chronic pain types with 26.1 points of pain reduction [21]. Further papers by Chen H. et al. 2016 and Vickers AJ et al. 2018 confirm the influence of „pricking" and „non-pricking" with sham acupuncture on therapy outcomes [22,23]. When combined with other therapies, there are also over-additive effects, as was shown in the study by France S. et al. 2014 in the combination of „dry needling" and conventional physiotherapy for the treatment of tension headaches (improvement up to 45 points) [24]. Also which form of acupuncture is used as „optimal

acupuncture“ has a direct impact on the effectiveness of the „acupuncture treatment“, which itself is not a uniform procedure. As an example, Wang L. et al. showed in their recent network meta-analysis that the most optimal form of acupuncture or stimulation for the treatment of non-specific chronic back pain (as measured by a 0-100 VAS and the Oswestry Disability Index) is the manual form of acupuncture combined with moxibustion (local heat stimulation) [25].

In addition, the majority of clinical trials to date do not investigate the co-therapeutic value of acupuncture to standard therapies or other e.g. TCM procedures anyway; although in the real world the multimodal treatment concept of chronic back pain is more the routine than the exception.

Also the implementation of a truly „blinding of outcome assessment“, i.e. masking the identity of the treatment group after randomisation to the assessor, is theoretically possible to overcome but usually very difficult to realise in everyday practice. It is therefore not surprising that precisely these quality dimensions lead to „high risk bias“ in the evaluation of studies. A possible consequence would be to use more comparisons of therapies with standard treatments as controls in order to avoid inappropriate placebo controls. But also here we have the problem of acceptance by the patients, who usually visit the acupuncturist to receive acupuncture and not to receive a conventional standard therapy, which has often already been used without success. Nevertheless, this seems to be a realistic form of study design for the performance audit as well. The health insurance model projects on acupuncture carried out in Germany between 2001 and 2005 were among other things also examined in comparison with standard treatment [26].

The most recent Cochrane review on acupuncture and chronic nonspecific low back pain from 11 December 2020 examined 33 RCTs with 8270 study participants, of which the majority, namely 7 studies with 5572 participants, came from Germany [27]:

Mu J, Furlan AD, Lam WY, Hsu MY, Ning Z, Lao L. Acupuncture for chronic nonspecific low back pain. Cochrane Database Syst Rev. 2020 Dec 11;12(12):CD013814. doi: 10.1002/14651858.CD013814.

The respective level of evidence of the studies examined was determined according to GRADE. In 7 studies with 1403 participants, the assessors found a pain reduction effect of -9.22 points (95% confidence interval -13.82 to -4.61 on a 0-100 VAS scale) between verum and sham acupuncture. The comparative assessment of pain reduction was made immediately after treatment (up to a maximum of 7 days afterwards = „immediate term“). The authors took -15 points on the VAS scale (or 30 percent relative pain reduction) as the clinically relevant threshold. However, for the assessment of the magnitude of clinical effects of pain and function the classification and evaluation according to a standard mean difference (SMD) could also be performed as follows [28]: Pain-reduction on a 0-100 VAS: small effect = 5 until 10 points (0.2-0.5 SMD), moderate effect = >10 until 20 points (>0.5-0.8), and large effect = >20 points (>0.8 SMD). According to this, moderate effects would already be assumed from >10 points on a 0-100 VAS. Smaller clinical effects (5-10 points) would not mean that a certain proportion of pain patients could not subjectively benefit from this therapy, especially in the case of long-lasting, chronic complaints. In this sense, smaller clinical effects with a low risk of adverse events and cost level of treatment are more justified in pain therapy [28]. Furthermore, the pain-reducing placebo comparison between acupuncture and sham acupuncture tends to underestimate the real effect size of verum acupuncture. The AHRQ (Agency for Healthcare Research and Quality of the U.S. Department of Health and Human Services) Review Update 2020 on the non-pharmacological treatment of chronic back pain, which uses the above effect scheme, therefore comes to the conclusion that acupuncture, compared to sham acupuncture and the usual standard therapy, shows a pain reduction with smaller effect sizes („pooled difference -0.54 on a 0 to 10 scale, 95% CI -0.91 to -0.16, I2=25%) immediately after the intervention [29]. Stratifying these overall results again by their control, the effect measures for the sham control with a „pooled difference -0.21, 95% CI -0.66 to 0.18“ in 4 studies are significantly lower than for the standard treatment with a moderate effect of a „pooled difference -1.01, 95% CI -1.60 to -0.28“ in 2 studies. There were no differences from controls in follow-up longer than 6 months but shorter than 12 months.

The Cochrane review finds no difference between the two acupuncture groups in a further 5 studies with 1481 participants with regard to the assessment of the subjective functional capacity of the back (by the Hanover Back Function Questionnaire) and therefore rates the evidence as „very low-certainty“.

The placebo or control problem described above once again led to an (expected) reduction in evidence and downgrading of the recommendation level of these studies. The authors conclude that acupuncture immediately after treatment did not relieve pain better than sham acupuncture; but worked better than no acupuncture treatment (e.g. waiting list control).

This reopens the debate about the role of acupuncture in pain management and an evidence discussion in relation to verum and placebo acupuncture. Although meta-analyses with 18000 patients published in 2012 and 2018

by Vickers et al. and the „Acupuncture Trialists' Collaboration" had already shown a superiority of verum acupuncture over sham acupuncture and control groups, this discussion remains controversial [23]. From a scientific point of view, this dispute will not end without new findings, e.g. on neurophysiology, about the effects of Sham acupuncture.

Nevertheless, the American College of Physicians already decided in 2017 to recommend certain non-pharmacological treatments, including acupuncture, as a „first line treatment" for acute and chronic back pain [30] and is again supported by the above-mentioned AHRQ in 2020 with regard to the necessary evidence [29]. This decision has certainly also been favoured by the „opioid crisis" in the USA, which is said to have caused an increase in opioid-related deaths from 9489 to 42245 between 2001 and 2016 [31].

Since 18 January 2020, even the statutory health insurance in America [„Center for Medicare and Medicaid Services (CMS)"] covers the costs for the treatment of acupuncture (also of Tai Chi) for non-specific chronic back pain. Reimbursement is for a maximum of 12 sessions of acupuncture each quarter and 20 sessions for the whole year [32].

In England, acupuncture for the management of chronic pain has also been recommended in the National Institute for Health and Care Excellence (NICE) guidelines since 2017 and once again in the April 2021 update according to the current evidence base [33]. Both guidelines conclude that there is superiority of verum acupuncture over sham acupuncture or standard therapy in reducing pain and improving quality of life [33].

If one considers the time it takes for a scientific idea or a product from the research laboratory to reach the medical guidelines of practical medicine, it takes on average 17 years [34], according to recent findings even 18 to 54 years [35]. So how long will it take the other way round until a procedure that has already proven itself in medical practice has found its recognition in research-based science? TCM seems to be still far away from this goal - despite all tradition and evidence. However, the worldwide TCM research efforts to date do deserve more acknowledgement than they are currently receiving from the EU's EASAC.

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