

homeopathic medicine selection, the 'symptom-cluster' approach was used: women first completed a questionnaire with symptoms representing keynotes of the homeopathic medicines. Women, whose symptom cluster matched the remedy picture of one of the homeopathic medicines were included in the trial. Other women were assigned to a parallel trial.

**Conclusions:** So far, positive clinical data have been obtained for the effectiveness and efficacy of homeopathic treatment in PMS. This line of research can act as an example on how to build up evidence for individualised homeopathic treatment in specific clinical conditions.

## Treatment of nervous complaints and exhaustion with the homeopathic medicinal product Manuia<sup>®</sup> - results of a cohort study

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**Background:** Exhaustion, nervousness and decreased physical and mental capability are recurrent challenges in GPs' daily routine. They are often resulting from overexertion, or disturbed sleep. Nowadays people feel exhausted and weak due to continuously increasing professional demands and rising challenges in daily life. The approved homeopathic medicinal product Manuia is used in the mentioned therapeutic area. It contains four single active substances: Damiana, Panax ginseng, Acidum phosphoricum and Ambra. So far, effectiveness and tolerability was confirmed by clinical experience, but systematically collected data were lacking.

**Patients and methods:** Between January and June 2011 the clinical effectiveness and tolerability of Manuia was systematically investigated in a prospective, multicentre, non-interventional cohort study. A total of 420 patients were observed by 76 German physicians in private practices. Median observation period was 24 days, median duration of symptoms since diagnosis 5 months.

As main outcome measure severity course of 20 symptoms (nervousness, irritability, sleep disturbances, hyperactivity, impaired concentration, listlessness, frustration, moroseness, exhaustion, dispiritedness, decreased capability, feeling of heteronomy, feeling lonely, feeling pressure to perform, feeling excessive demands, forgetfulness, gastrointestinal complaints, cardiovascular complaints, muscle tension, headache) was evaluated with a 5-item score (0 = not present; 4 = very severe). In addition physicians' Clinical Global Impression (CGI), patients' quality of life and ability to actively attend different domains of daily's life, and tolerability of Manuia were documented.

**Results:** The sum score as well as the severity of each single symptom decreased significantly during the observations' period ( $p < 0.01$ , paired t-test). Illness severity measured by CGI decreased significantly ( $p < 0.01$ , McNemar test; CGI 4-7: 71.7% to 35.2%). Ability to work and to attend social and family life improved significantly ( $p < 0.01$ , McNemar test). In 77.1% (n=324 out of 420) of the patients quality of life was good, very good or excellent during control visit, compared to 15.8% (n=66 out of 420) at baseline. 92.4% of the patients rated their condition as improved, 64.1% as much or very much improved. Median duration until onset of action was 7 days. Tolerability was good or very good in 98.1% of all cases.

**Conclusion:** The study data underlined the existing good clinical experience with Manuia and suggests Manuia as a therapeutic option in the treatment of nervous complaints and exhaustion. Further controlled studies are necessary to confirm these findings.

## Might evaporation-induced droplet patterns serve in agro-homeopathic research and support experimental trials?

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Agro-homeopathy provides numerous solutions for a sustainable agricultural production, like for instance cost-saving and residue-free treatments for yield improvement and management of diseases and pests. However, one of the main difficulties in this approach is the right treatment choice (i.e. the curative principle and its dilution level) that often requires numerous time & cost consuming experimental trials.

In the present experiment we applied the droplet evaporation method, previously developed by our research team for wheat quality analysis, to test the influence of highly diluted homeopathic treatments (HD) of *Arsenicum album* on both healthy and previously arsenic trioxide stressed wheat seeds (isopathic model). The pattern evaluation of the resulting polycrystalline structures consisted in (i) the calculation of their local connected fractal dimension, known to reflect the pattern complexity, and (ii) in the fluctuating asymmetry measurement, known to be inversely correlated with the symmetry exactness of the structures, and thus also the vitality of the sample. In polycrystalline structures formed under the same conditions these two measurements have been found to reflect the sample health. Additionally, in order to support the crystallographic data with traditional analysis methods for seed viability, we performed the seed germination test and measured the shoot

lengths: our results show that the complexity and symmetry of polycrystalline structures correlates with the viability of non-stressed and stressed wheat seeds following *Arsenicum album* HD with respect to control.

These first results indicate that the droplet evaporation method might constitute a support for experimental trials and/or a pre-screening method for treatment test, since it shows to be sensitive to the sample vitality.

**Keywords:** Droplet evaporation method, Polycrystalline structures, Bilateral symmetry, Fractal dimension, Arsenic trioxide, Ultra high dilutions

## Model validity of randomised placebo-controlled trials of individualised homeopathic treatment

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**Purpose:** A new programme of systematic reviews of randomised controlled trials (RCTs) of homeopathy distinguishes several key attributes of study design and quality: placebo controlled *cf.* other-than-placebo controlled; individualised *cf.* non-individualised homeopathy; treatment *cf.* prophylaxis; internal validity *cf.* model validity. The present phase of the review programme focuses on assessing the model validity (MV) of peer-reviewed, placebo-controlled, RCTs of individualised homeopathic treatment.

**Methods:** A systematic literature search and subsequent reappraisal of retrieved records identified 31 RCTs that satisfied the inclusion criteria for the present study. MV of the eligible RCTs was appraised using a novel criterion-based method. Assessment domains address: (i) the rationale for the choice of the particular homeopathic intervention; (ii) the homeopathic principles reflected in the intervention; (iii) the extent of homeopathic practitioner input; (iv) the relevance of the main outcome measure; (v) the capability of the main outcome measure to detect change; (vi) the length of follow-up to the endpoint of the study. These six MV domains per RCT were categorised by each of three independent assessors as 'acceptable', 'unclear' or 'unacceptable', disparities of opinion being resolved by consensus discussion.

**Results:** Domain-specific and overall ratings of MV per RCT await the outcome of ongoing consensus discussions. A full set of findings will be presented at conference.

**Conclusions:** MV data contribute importantly to the appraisal of RCT quality in systematic reviews of homeopathy.

## Study of Gelsemium sempervirens in a neurocyte model. An update

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Previous investigations showed significant anxiolytic-like activities of *Gelsemium sempervirens* L. (*Gelsemium s.*) in mice models. To provide new insights into the neural substrates of anxiety and to identify drug targets, we decided to investigate the *Gelsemium s.* mechanism of action in neuronal models by assessing the genome expression changes. The SH-SY5Y and IMR-32 human neuroblastoma cells were used since are widely employed in neuropharmacology and well characterized. The drugs were produced by Boiron Laboratoires (Lyon), starting from a whole-plant-hydroalcoholic extract and the cells were treated with 6 increasing dilutions 2c, 3c, 4c, 5c, 9c, 30c. We compared the drug effects with those of control solutions prepared by the same procedure, but with the solvent vehicle without the plant extract. All dilution steps were followed by strong succussion. Final ethanol concentration was 0.03% v/v. After having ruled out possible toxic effects of any test solution on cell viability, we evaluated gene expression firstly by using a microarray designed for the whole human transcriptome (Nimblegen, Roche). We used the Limma statistics approach (n=4 biological replicates) to select a set of differentially expressed genes and Friedman test followed by Wilcoxon signed-rank test to check the null hypothesis that high dilutions have no effect in this model. The exposure to 2c dilution promoted a small (fold changes between 0.5 and 1.0) but significant down expression of 49 genes as compared with untreated controls. With higher dilutions, most of the genes down-regulated in the 2c-treated samples were also under-expressed in 3c and, to a varying extent, even in higher dilutions. No changes of housekeeping genes were recorded, confirming the specificity of drug action. The changes in the 49 selected genes of SH-SY5Y cells were in the same direction in the IMR32 cells, showing that the expression of the same gene set was also modified in a second type of neurocyte. Afterward we performed the RT-qPCR on a subgroup of relevant genes modulated in 2c treatment (i.e. transcription factors, G-protein coupled receptors or neuropeptides) and we confirmed the down-regulation for the genes DDI1, EN2, GALR2, GPR25, OR5C1, Kikbl4 and TAC4. In the Wilcoxon analysis, applied to the 49 genes, the number of down-regulated ones was systematically higher than the number of genes with positive fold change over all dilutions (p<0.0001). No significant differences between treatments and controls in a randomly chosen gene set of 49 genes were observed, suggesting that the *Gelsemium s.* effects are not due to chance. In parallel we