

## ORIGINAL PAPER

# Assays of homeopathic remedies in rodent behavioural and psychopathological models

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The first part of this paper reviews the effects of homeopathic remedies on several models of anxiety-like behaviours developed and described in rodents. The existing literature in this field comprises some fifteen exploratory studies, often published in non-indexed and non-peer-reviewed journals. Only a few results have been confirmed by multiple laboratories, and concern *Ignatia*, *Gelsemium*, *Chamomilla* (in homeopathic dilutions/potencies). Nevertheless, there are some interesting results pointing to the possible efficacy of other remedies, and confirming a statistically significant effect of high dilutions of neurotrophic molecules and antibodies. In the second part of this paper we report some recent results obtained in our laboratory, testing *Aconitum*, *Nux vomica*, *Belladonna*, *Argentum nitricum*, *Tabacum* (all 5CH potency) and *Gelsemium* (5, 7, 9 and 30CH potencies) on mice using ethological models of behaviour. The test was performed using coded drugs and controls in double blind (operations and calculations). After an initial screening that showed all the tested remedies (except for *Belladonna*) to have some effects on the behavioural parameters (light–dark test and open-field test), but with high experimental variability, we focused our study on *Gelsemium*, and carried out two complete series of experiments. The results showed that *Gelsemium* had several effects on the exploratory behaviour of mice, which in some models were highly statistically significant ( $p < 0.001$ ), in all the dilutions/dynamizations used, but with complex differences according to the experimental conditions and test performed. Finally, some methodological issues of animal research in this field of homeopathy are discussed. The “*Gelsemium* model” – encompassing experimental studies *in vitro* and *in vivo* from different laboratories and with different methods, including significant effects of its major active principle gelsemine – may play a pivotal role for investigations on other homeopathic remedies. *Homeopathy* (2009) 98, 208–227.

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## Introduction

Anxiety and behavioural disorders have a high prevalence in modern society, and consume significant

financial resources. The most well-known tranquilisers or anxiolytics are those of the benzodiazepine family (BZDs), which act by modulating the GABAergic receptors, but many others are known, including Buspirone and other drugs belonging to the class of azaspirodecanedione compounds, which act as agonists of the serotonergic receptors (5-HT<sub>1A</sub>). However, the clinical use of conventional drugs is not without its drawbacks, particularly due to side effects such as psychomotor impairment, potentiation of other central depressant drugs, and induction of forms of dependence that are difficult to reverse. Natural

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remedies possessing the same efficacy as allopathic drugs, but with fewer side effects, would be a valuable addition to the treatment options for anxiety-related disorders.

Research in anxiety has a long history of development of animal models. Murine models are the most frequently used, and explore various aspects of anxiety, often making use of defensive behaviours. The measurement of anxiety-related behaviour in animal models is based on the assumption that anxiety in animals is comparable to anxiety in humans. Although it cannot be proven that animals experience anxiety in the same way as human beings, it is generally undisputed that certain behaviours of rodents in experimental conditions correspond to central and peripheral emotional responses to acute or protracted stress. Hormonal and neuromediator variations are common to humans and animals and, most importantly, drug responses in animals are often predictive of the response in human clinical studies, or at least suggest novel pharmacological approaches.

Animal models have greatly assisted in understanding the development of disease at the tissue, cell and molecular level. They have also helped to elucidate the mechanisms of absorption, distribution, transformation and excretion of drugs, thereby allowing the active ingredients of medicinal plants and animal products to be identified. With allopathic drugs, dosages and adverse reactions are generally studied in animal models prior to undertaking human trials. In homeopathy, the opposite has been true: trials on humans have only recently been followed up with tests on animals.

A number of animal models have been used to investigate the action of diluted/succussed (potentised) homeopathic remedies. In this work, we will focus on the experimental (murine) models of anxiety and other neurological or behavioural disorders that are in some way correlated with anxiety. To the best of our knowledge, this is the first systematic review of homeopathic research in this field.

The advantage of animal tests is that they allow testing of multiple dilutions/dynamizations, compared to a vehicle, under reliable, reproducible and valid conditions. Different experimental models can be tried out on groups of animals to identify which one is most responsive under particular conditions. As well as offering a preclinical indication of the possible efficacy of new remedies, another goal of basic research in homeopathy is to study the mechanism of action of remedies. Here, the two major themes under investigation are: (a) the mode of action of the 'simile' effect, i.e., how a substance known to have pathogenetic effects in healthy organisms (cells, animals, humans) can act as a therapeutic agent in diseased organisms and (b) the 'high-dilution' effects, i.e., the question of whether and how substances diluted (and dynamized) to the point that few or no molecules of active ingredient remain can have biological effects. These two themes can in turn be split into a number of narrower questions regarding the methods of dilution, the most valid model for investigating the effect, the type of solvent used (distilled water, saline solutions, water/ethanol mixtures), and other technical details that may often affect the final outcome.

This paper is divided into two sections: the first provides an overview of the international literature on animal models for studying homeopathy in the specific field of anxiety disorders and other correlated behavioural disorders, while the second describes recent experiments conducted in our research laboratory on the behaviour of mice exposed to homeopathic remedies potentially capable of modulating anxiety and emotional responses to novel environments.

Because the existing literature on this subject is very varied and largely preliminary, with many reported observations not subsequently confirmed by other authors, it is important to adopt models that have already been validated by the pharmacological literature, as well as highly rigorous experimental conditions (blind protocols, reproducible preparation methods, sufficient numerosity) and solid statistics.

To provide a meaningful model of human behaviour, an animal test must meet three criteria: predictivity of responses to drugs, face validity (meaning that the phenomenological aspect – e.g., agoraphobia, neophobia, avoidance of threatening places – is observed also in humans) and construct validity (similar aetiology and triggering factors). In experimental tests, animals are placed in situations involving exploration, conflict between desire and punishment, conditioned fear and aggression. Exploring an environment consisting of light and dark zones, or the situation of being suddenly placed in a novel environment, elicits a conflict between approach and avoidance that allows different responses to be measured in a controlled manner. Mice tend to prefer dark, enclosed spaces to large, well-lit arenas, and the amount of time they spend in the dark zone, or the number of transitions between light and dark, are sensitive to benzodiazepines and to the agonists of serotonergic receptors, in a manner that correlates well with clinical efficacy in humans.<sup>1</sup> There are also many other experimental approaches to studying animal behaviour, some of which will be described in this review, and genetic models (hitherto not used in homeopathy) have also recently been introduced. Animal models of anxiety can be grouped into two main subclasses<sup>2</sup>: the first involves the responses of animals conditioned with stressful and often painful events (e.g., exposure to electric shocks, forceful containment in small spaces), while the second involves the study of unconditioned responses using ethological paradigms and spontaneous reactions to non-painful stimuli (e.g., exposure to a novel highly illuminated test chamber or to an unfamiliar open field (OF)).

Our general hypothesis is that complex models of animal behaviour, in which different symptoms are evaluated in situations where the animal is not particularly stressed, are able to sensitively detect 'pathogenetic' or 'therapeutic' signs. After identifying the remedies that are effective in the chosen model, and ascertaining the reproducibility conditions and the most active dilutions, it is possible to proceed to study the mechanisms of action with a greater likelihood of obtaining consistent results.

Ethological observations show that, though rodents naturally tend to explore a novel environment, OFs are aversive

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