Behavioral Research with Homoeopathic Remedies from Plant Extracts: Biases and Comments

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My opinion

Complementary and alternative medicine (CAMs) in behavioural science has raised several comments, due to the presence of a placebo/nocebo response (Davidson et al, 2011; Chirumbolo, 2011; Bellavite, 2011; Paris A, 2011); this issue represents a puzzling question for behavioural science, because placebo effects, in randomized placebo-controlled clinical trials (RCTs) on classical homeopathy, have shown not to be larger than placebo effects in conventional medicine (Nuhn et al, 2010). In this perspective, placebo response appears rather significant in a behavioural or psychiatric clinical outcome and prompts to suggest an obvious question: do commercial homeopathic remedies act simply by a placebo mechanism or not? Researchers tried to overcome this snag by considering animal models. However, a placebo/nocebo response has been shown also for laboratory animals (McMillian, 1999; Enck et al, 2008) and biases in experimental settings are always in ambush. Actually, a further exploration about the nature of the placebo responses in clinical trials has to be made and, moreover, major questions for future research such as the relationship between expectations and conditioning in placebo effects, which have been shown in animals, the existence of a consistent brain network for all placebo effects, the role of gender in placebo effects, and the impact of getting drug-like effects without drugs, have to be addressed (Enck et al, 2008)

Biases in this context may arise. The use of very diluted solutions of plant extracts, such as Gelsemium sempervirens, an approach which was called erroneously as nanopharmacology (Bellavite, 2011; Seifulla, 2010), includes ethanol in the experimental setting. A recently reported commentary maintained that the anxiolytic effect of diluted doses of Gelsemium sempervirens did not provoke any sedation side-effect (Bellavite et al, 2009; Magnani et al, 2010). Although some reports has shown that low doses of ethanol might increase the locomotor activity in mice, recent reported evidence in rats suggested that this dose of alcohol may result in possible sedation, though injected in different times. In rats a dose of 0.25 g/kg EtOH has been shown to be the lowest dose able to decrease significantly locomotion in these rodents (Chuck et al, 2006). Whether considering as 500 g the mean body weight of a male subject, this dose should correspond to 125 mg of alcohol; a male mouse is about 1/25 of a male rat, so a mouse receiving about 5 mg of alcohol, might undergo comparable sedation effects. The experimental setting planned and performed by some authors used ethanol in each tested sample, including controls; this should assure that sedation would be carried throughout the analysis, without influencing the net outcome of the overall experiment. Bias arises because ethanol is a pharmacological compound as like as gelsemine or buspirone (Bellavite et al, 2009; Magnani et al, 2010). Rodents response to ethanol may be highly variable, as like as humans (Fraser et al, 1995), because of the intra-individual variability in detoxifying enzymes and non-linear BK channels function (Nelson et al, 2004; Treistman et al, 2009); its pharmacokinetics is complex, it does not depend on mouse strain and administration route, it has a dose-dependent linear increase in alcohol concentration in the plasma and brain and non linear or parabolic increase in the area under ethanol pharmacokinetic curve in tissues (Golovenko et al, 2001). In the experimental conditions reported elsewhere by others (Bellavite et al, 2009; Magnani et al, 2010), it is quite difficult to assess if ethanol might exert a significant effect on pharmacokinetics of other drugs such as ergot alkaloids contained in Gelsemium plant extracts, but what it is well known is that ethanol possesses a significant influence on plasma pharmacokinetics of any drug, in a general way (Lennernas, 2009).

Furthermore, the effects of ethanol are often biphasic (stimulatory/inhibitory) as like as low doses of a plant extract (Calabrese, 2008), so rendering more complex any possible interpretation of the assay (Middaugh et al, 1987; Crabble et al, 1982). The association of ethanol with a different drug might change dramatically the fashion by which the drug operates in the behavioral test and a molecular or cellular comparison.
with the same molecule diluted into water (Bellavite, 2011; Venard et al, 2009) should not have been made, unless considering the introduction of a set of controls without ethanol.

Furthermore, within this experimental condition open field test (OFT) and light-dark box test (LDT) were unable to discriminate sedation or anxiolyis by evaluating locomotor or exploratory activity by alone; furthermore, the reference control buspirone, showed sedation side effects (Magnani et al, 2010; Bellavite, 2011). On the contrary, Venard and colleagues do not include ethanol by no means in their research and the experimental approach dealt with an in vitro research on mice tissue slices (Venard et al, 2009). Gelsemium sempervirens Ait, alcoholic extract contains many other ergot alkaloids besides gelsemine, most of which exert many depressant and sedative effects (Duke, 1992; Gahlot et al, 2011). Furthermore, when low doses of a plant-derived compound are used, hormetic effects may arise. Hormetic mechanisms have been described by using a broad panel of behavioral tests; the analysis revealed that hormetic-like biphasic dose-response were commonly observed across all screening tests (Calabrese, 2008). These issues normally hamper a clear description of the anxiety-like behavior in tested animals, especially if environmental conditions are considered (Lewejohann et al, 2006). For example, dark box in LDT may be felt by mice as an aversive environment, so forcing the animal in spending more time in the lit arena and the lit area, if has the same light exposure of the whole environment, might do not elicit any aversive stimulus (Magnani et al, 2010; Hascoet and Bourin, 1998; Bourin and Hascoet, 2003). These considerations appear very interesting when anxiety models are addressed with laboratory animals. Which is anxiety in laboratory rodents? Is the term anxiety interchangeable with fear, stress, panic or danger sensitivity? In animals, fear is an adaptive response that has evolved to provide protection from potential harmful environments. and fear-related behaviors in mice have long been investigated as potential models of anxiety disorders (Hettema et al, 2011). When fear is disproportionate in facing the harmful situation, it can lead to an anxiety disorder (Graham et al, 2011). In laboratory animals, such as mice or rats, fear may be acquired when a neutral conditioned stimulus is paired with an aversive unconditioned stimulus and, usually, after several such pairings, the subjects is able to learn that the conditioned stimulus elicits several fear responses: in this circumstance, anxiety may arise (Graham et al, 2011). This possibility occurs when the same operator makes serial injections and performs behavioral tests (Magnani et al, 2010). Several reports dealing with herbal extracts in animal anxiety models are limited to the simplest standardized behavioral tests, which are indicated to measure locomotion and exploratory tendency as main parameters of a non-anxious behavior: in this context a decrease in these two parameters might be associated with other hallmarks, such as sedation or depression, then demonstrating that the complex mixture of compounds contained in the alcoholic plant extract may show many different pharmacological effects. Pavlovian conditioning paradigms have become important model systems for understanding the neuroscience of behavior, especially in rodents. In particular, research about the extinction of Pavlovian fear responses is yielding important information about the neural substrates of anxiety disorders, such as phobias and post-traumatic stress disorder (PTSD), even in humans. An advantage of the fear extinction model is that comparison of animal studies should suggest a considerable similarity between the neural structures which are involved in extinction in rodents and in humans. These studies allow to understand the neural mechanisms underlying behavioral interventions that suppress fear, including exposure therapy in anxiety disorders (Chung et al, 2009). Fear and anxiety appear, therefore, as two different and strictly related paradigms in neuroscience. In laboratory, several behavioral tests are available to ascertain if the researcher is investigating a fear extinction mechanism, an anxiety disorder or an extinction of both, due to a pharmacological treatment. One good test is elevated plus-maze. Fear can be measured as a decreased percentage of time spent on open-arm exploration in the elevated plus-maze and can be potentiated by prior inescapable stressor exposure, although not by escapable stress. In this case, the application of fear-potentiated plus-maze behavior has several advantages as compared to more traditional animal models of anxiety, such as LDT or OFT (Magnani et al, 2010). The traditional, elevated plus-maze is able to measure innate fear of open spaces but a fear-potentiated plus-maze behavior should reflect an enhanced anxiety state, called as allostatic state. This typical "state of anxiety" can be defined as an unpleasant emotional arousal in face of threatening demands or dangers (Korte and De Boer, 2003). Actually, a cognitive appraisal of threat is a prerequisite for the experience of this type of emotion. Another hallmark of this test is that depending on the stressor used this enhanced anxiety state can last from 90 min to 3 weeks. Stress effects are more severe when animals are isolated in comparison to group housing. In such a system drugs can be administered either in the absence of the original
stressor or after stressor exposure. As a consequence, retrieval mechanisms are not affected by drug treatment. This fear-potentiated plus-maze behavior is sensitive to proven/putative anxiolytics and anxiogenics which act via mechanisms related to the benzodiazepine-gamma-aminobutyric acid receptor, but it is also sensitive to corticotropin-releasing receptor antagonists and glucocorticoid receptor antagonists and serotonin receptor agonists/antagonists complex (Korte and De Boer, 2003). For those reasons, fear-potentiated plus-maze behavior is very robust, experiments can easily be replicated in other labs and the mechanism can be measured both in male and female individuals. In this strategy, neural mechanisms involved in contextual fear conditioning, fear potentiation and state anxiety can be studied, so rendering fear-potentiated plus-maze behavior a valuable measure in the understanding of neural mechanisms involved in the development of anxiety disorders and in the search for novel anxiolytics (Korte and De Boer, 2003; Korte and De Boer, 1999; Korte and De Boer, 1999). This assumption would like to suggest to better evaluate different behavioral tests in investigating anxiety-like models in animals, attempting to elicit biases at the lowest frequency possible, not to create a possible “integrate behavioral assay” (Bellavite, 2011). For the many reasons previously indicated, the interpretation of behavioral tests includes many tricky issues, which asks for further investigation (Chirumbolo, 2011).

CAMs in psychiatry or behavioral disorders, while accounting on animal models derived evidence, may contain biases due to the high complexity of the addressed issues. Statements and comments about the possible effectiveness of low concentrated alkaloids from alcoholic plant extracts have to be reappraised and evaluated at the light of bias analysis (Podsakoff et al, 2003). Anxiety-like models in laboratory animals such as rodents contain many unresolved and puzzling aspects that merit to be explained by using increasingly sophisticated approaches, aiming at not lapsing into easy conclusions.

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