The Medicine Cabinet: Placebo or Nocebo

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These Latin terms for 'I please' or 'I harm' underlie common significant difficulties and complexities in treating children with medications. For example, in depression a third of young people respond to 'pink medicine' (a traditional form of placebo medication) whereas two thirds respond to an antidepressant. In effect, we don't know whether the medication has worked, or whether they would have got better anyway. And yet there is still one third that has failed to respond. Fortunately, it is found that on a second antidepressant another two thirds will respond, leaving a yet smaller group who still need further treatment. Overall, the placebo effect of any treatment tends to get less, the more severe and persistent a condition is.

This situation gets more complex if, as commonly occurs, the child and family report a medication works for 3 weeks or 3 months and then no longer works. Was this a placebo effect for the first period, or just part of a natural variation of the symptom over time or is it due to some sort of accommodation to the effect of the medication, through a pharmacological, neurotransmitter mechanism, metabolic or pharmacokinetic mechanism? All these are scientifically shown to be possible but very difficult to distinguish as it is not possible to do tests on these options in an individual patient.

In contrast, in a recent randomised control study of fluoxetine in children and adolescents with Autism, 45% of the fluoxetine group experienced adverse events or side effects but this was not statistically significantly different to the 42% of the placebo group who also experienced adverse events or nocebo effects or negative placebo. Common adverse reports for fatigue, anxiety, nausea, headaches, sleeplessness, skin rash occur in both groups, meaning that side effects occur as much on no active treatment as on active treatment. Indeed, these are common everyday experiences even if you are not unwell or having treatment.

Thus, how do you know a negative effect is a result of a misinterpretation or some sort of persuasive process in examining one's own wellbeing rather than due to an effect of the medication? Particularly if a patient or parent comes to the consultation with a suspicion or pre-conviction that psychotropic medications are harmful and people should get better from illness without medication, then such anxiety or thinking becomes a causal factor in getting such nocebo symptoms. I recall a patient with severe anxiety and severe tics or Tourette's syndrome, whose mother was suspicious and sceptical about medication. Every side effect that the parent was warned of, the patient dutifully complained about. This lack of trust in the potential of a medication to help, led to premature breakdown in treatment in the context of other complex family social adversities that were also difficult to influence. This illustrates the level of trust a child and family need to

have for their clinician's judgement and the possibility that a medication can be helpful. If side effects occur, the child, family and clinician need to examine the seriousness and significance openly together, being aware of both placebo and nocebo effects. People often show greater sceptism or anxiety about a psychotropic medication than for a medication for a somatic disorder albeit they may be subject to the same level of scientific evidence. The article below describes the complexity to some of the mechanisms of placebo and nocebo, which clinician and patient need to be aware of to get the optimal benefit from treatment and to minimise nocebo effects.

Placebo or Nocebo by Judy Longworth

Definitions:

Placebo: Google describes it as a medicine or procedure prescribed for the psychological benefit to the patient rather than for any physiological effect; a substance that has no therapeutic effect, used as a control in testing new drugs (Google, 2018)

Nocebo: a detrimental effect on health produced by psychological or psychosomatic factors such as negative expectations of treatment or prognosis (Google 2, 2018).

The term placebo is often used in relation to something that has an effect, even a therapeutic effect, however that "something" should be inert. Placebo effects are a recent area of study and with more understanding there could be better clinical trial research. Clinical trials are the backbone of evidence based medicine and thus with the recognition of best practice and evidence based practice the understanding of placebos and nocebos has increased.

Traditionally, placebo is seen as an inert or "inactive" substance or procedure and the placebo effect (or response) is something that follows on from the administration of the placebo. There is a paradox in that an inert substance should not elicit a response or effect on patient's mind, brain or body. The association of placebo effects with randomised controlled trials (RCTs) has caused confusion because the response in the placebo group is not necessarily a genuine psychosocial response to the simulation of treatment. The response to a placebo in RCTs might reflect the natural course of disease, fluctuations in symptoms, regression to the mean, response bias with respect to a patient reporting subjective symptoms and other concurrent medications (Finnis et al, 2010). To better understand placebo effects in clinical trials and practice, a shift in focus from the inert substance to what is actually happening for the patient is a good place to start. Does the literature suggest that the placebo effect is a genuine psychobiological event attributable to the overall therapeutic context? Understanding this leads to a better clinical trial and stronger basis for evidence based medicine. These will be discussed later in this article.

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Before a medication can be marketed or licensed it needs to fulfil certain regulatory requirements. The FDA (USA Federal Drug Administration) wants the sponsor, usually a pharmaceutical company, to show through adequate and well-controlled clinical studies the superiority of one substance or procedure over another. This also applies to the TGA (Therapeutic Goods Administration) in Australia. A well controlled study involves a comparison of subjects treated with the new medication and a suitable control population so that the effect of the new medication can be seen without influences such as spontaneous change, placebo effects, concomitant medications or observer expectations. Placebo control, no-treatment control (suitable where objective measurements are felt to make blinding unnecessary), and dose-comparison control studies are all study designs in which a difference is intended to be shown between the test article and some control (FDA, accessed 2018).

The FDA wants a new medication to show superiority over the control substance. If the control or inert substance is unable to show superiority then there would be no licensing and hence marketing of the product. This would be a problem for trials that are comparator trials i.e. trials against a product that was already licensed/marketed as the difference between comparator and new substance might not be statistically different to lead to approval by the governing authority.

Why placebo controlled trials?

One way as discussed to show superiority is by placebo controlled trials. There is an ethical question regarding whether clinical subjects should be 'washed out' from their current active medication and then randomly assigned to a treatment arm that might consist of a placebo (or inert substance) exposing the subject to significant risks, especially when there is available efficacious approved medications. There are advocates for the approach that new medications should be approved for clinical trials that compare the investi-

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gational medication with established approved medications. These trials are often done post marketing by research institutes instead of the traditional pharmaceutical company trials. This research approach is called equivalence or non-inferiority and is in contrast with current criteria of the FDA for superiority.

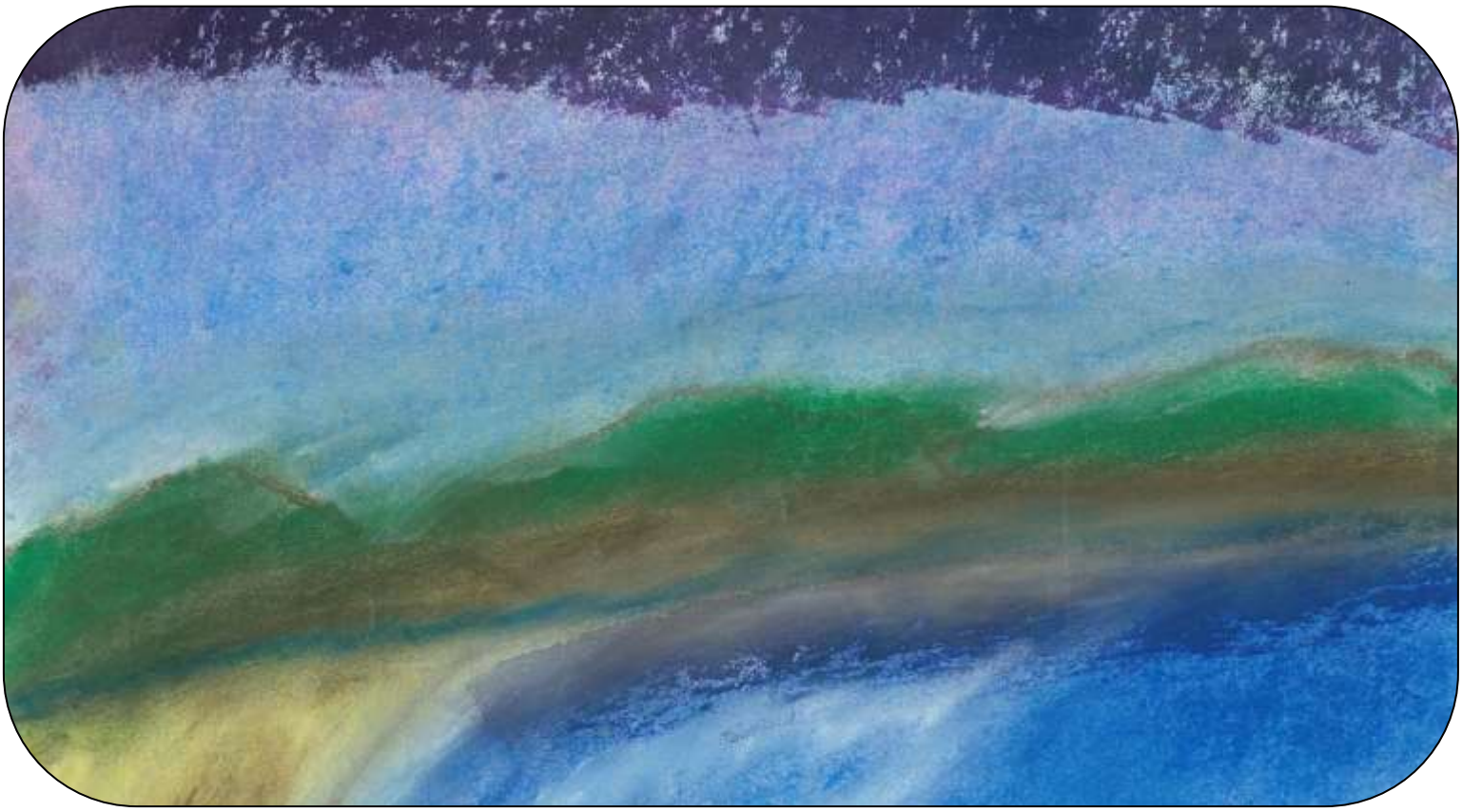
One limitation of placebo trials, especially when these are only being used for the licensing of medication, is that there is no comparison with conventional medication; i.e. equivalence studies when applying the results to the conventional or normal population (Krauss, 2018). These trials are used for bodies such as the Pharmaceutical Benefits Advisory Committee (PBAC) when deciding about pricing of medications to go onto the Pharmaceutical Benefits Scheme (PBS). Superiority studies are necessary for the investigational medication to show prominence over the comparator, thus for practical reasons the comparator is always placebo.

Placebo trials

The neurobiology of placebo responsiveness has addressed placebo analgesia, and is considered in terms of opioid and non-opioid mechanisms. The use of naloxone (opioid antagonist) in studies has shown the involvement of endogenous opioids in some placebo effects. Placebo analgesic effects are also likely to be inhibited by cholecystokinin as trials with cholecystokinin antagonist have shown a potentiated effect (to increase the power of the drug). Cholecystokinin has a key role in nocebo hyperanalgesia which occurs through anxiety mechanisms including the hippocampal regions. Neuroimaging studies have shown nocebo affects brain activation in different sites to placebo’s (Finnis *et al*, 2010).

Understanding how a placebo works clinically in different patient groups over time has not kept pace with research into the mechanisms of placebo effects which have mainly been laboratory experiments rather than those in a clinical setting (Finnis *et al*, 2010). There have been several clinical trials in adults showing the clinical relevance and aetiology of placebo-induced somatic sensations in irritable bowel syndrome and allergic rhinitis. The allergic rhinitis study (Schaefer *et al*, 2018) showed that placebos without deception can improve symptoms of allergic rhinitis and especially the quality of life but no effects on the improvement of symptoms.

Clinically focused research is needed to explore non-deceptive techniques for prescribing treatment aimed at promoting placebo effects; there has been some progress as there is clinically relevant evidence show-



Pain	Activation of endogenous opioids and dopamine (placebo; activation of cholecystokinin and deactivation of dopamine (nocebo)
Parkinson's disease	Activation of dopamine in the striatum and changes in activity of neurons in basal ganglia and thalamus
Depression	Changes in electrical and metabolic activity in different brain regions (eg ventral striatum)
Anxiety	Changes in activity of the anterior cingulated and orbitofrontal cortices; genetic variants of serotonin transporter and tryptophan hydroxylase
Addiction	Changes of metabolic activity in different brain regions
Autonomic responses to brain stimulation	Change of neuronal excitability in limbic regions
Cardiovascular system	Reduction of β adrenergic activity of heart
Respiratory system	Conditioning of opioid receptors in the respiratory centres
Immune response	Conditioning of some immune mediators (eg, interleukin 2, interferon Ɣ, lymphocytes)
Endocrine system	Conditioning of some hormones (eg growth hormone, cortisol)
Physical performance	Activation endogenous opioids and increased muscle work
Alzheimer's disease	Prefrontal executive control and functional connectivity of prefrontal areas

Table of Mechanisms for placebo effects in medical conditions and physiological by Finnis et al, 2010.

ing placebo effects can have therapeutic effects in different populations (Finnis *et al*, 2010).

Hall and colleagues consider the possible interaction between placebo and drug molecular pathways, especially the genomic effects, and the implications for randomised control trial studies (Hall *et al*, 2015). This leads to the probability of identifying potential responders and non-responders through their genetic profile. The first evidence that there is a biological process giving rise to the placebo response which is more than just pleasing the experimenter was published in 1978 involved a series of molar teeth extraction and pain control experiments.

Placebo effects

Placebo effects are often considered as innocuous but this can be misleading as improvement in patient's symptoms that can be attributable to their participation in the therapeutic encounter with all its interactions (Kaptchuk and Miller, 2015). Placebo effects have been shown to rely on complex neurobiological mechanisms involving neurotransmitters such as endorphins, cannabinoids as well as dopamine (Kaptchuk and Miller, 2015). There has even been fMRI studies which show the areas in the brain affected and these include the prefrontal cortex, anterior insula, rostral anterior cingulate cortex, and amygdala (Tetreault *et al*, 2016). There has also been genetic studies showing different alleles of genes displaying different responses such as different allele polymorphisms in the COMT (enzyme important in dopamine synthesis) studies in irritable bowel syndrome (IBS).

Finniss and colleagues have produced a table of mechanisms for placebo effects in medical conditions and physiological systems as replicated above (Finnis *et al*, 2010).

Nocebo effects

Less is known about the mechanism for nocebo response which can also be quite anxiogenic and stressful and thus limits ethical research into this mind-brain interaction. Study of nocebo effect relates to the nega-

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tive psychosocial context surrounding the treatment. As for placebo, it is the administration of an inert substance together with the suggestion that the substance will do harm. Nocebo-related effect also refers to the negative expectation of symptoms worsening with the administration of an inert substance. Most of this research has been done in pain where the negative expectations can lead to an amplification of pain response.

More recent studies have found nocebo effects were also associated with a decrease in dopamine and opioid activity in the nucleus accumbens, thus reducing the role of the reward system in nocebo effects as well. This suggests there is a complex relationship between different neurotransmitters such as dopamine and opioids when either placebo or nocebo are administered (Enck *et al*, 2008). Further to this, one suggestion of negative information can induce long-lasting negative effects (Colloca and Finniss, 2012).

The way information is delivered with regards to disclosure of potential adverse events in the clinical setting has been highlighted in several clinical trials involving significant nocebo responses (Colloca and Finniss, 2012). Nocebo effects can modulate the outcome of a given therapy in a negative way as do placebo effects in a positive way (Colloca and Finniss, 2012). Thus, the way information is delivered can have major implications on the results of an intervention.

The placebo-nocebo effects are just being recognised and as further studies are done more information will come to light as well as confirming studies that have already been done. The nature of how we test new medications in clinical trials will also change with new studies in pharmacogenomics and the impact of our genome on our response to medication. When looking at these issues in respect to children and adolescents there are further ethical considerations to be made. Studies in RCTs on the same active medication has shown adults and children have varied placebo response rates (Weimer *et al*, 2013). It has been noted in a review that placebo responses in children with psychiatric conditions (major depression, obsessive compulsive disorder and other anxiety disorders) when pooled are higher than those known in adults (Weimer *et al*, 2013).

There is the assumption that placebo response is mainly generated by two distinct mechanisms: expectancies on one hand and Pavlovian conditioning on the other. In adolescents, these can be assumed as well as instrumental learning and learning by imitation as well as the genetic contribution (Weimer *et al*, 2013). Clinical trials are beginning to acknowledge that the higher placebo response especially in paediatric depression trials might not be attributable to most known factors such as amount of contact with staff or chances of receiving active treatment as it is in adult studies and further studies are needed into the cause of the placebo response.

In light of the paucity of placebo studies in children and adolescents there should be more studies as well as the need for gender studies as well as genetics to cover confounders.

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