

Sertraline or placebo in chronic breathlessness? Lessons from placebo research.

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We were fascinated by the recent paper from Currow and colleagues [1] which described the largest randomised controlled trial of an antidepressant in the treatment of chronic refractory breathlessness. This study was important as there are few pharmacological treatments available for chronic breathlessness. In this group there is an unmet clinical need for treatments that target symptoms. The study's theoretical basis was well supported by preliminary data. However, no difference was observed between sertraline and placebo for the primary outcome measure, the improvement in breathlessness intensity.

We are particularly interested in the observation that breathlessness intensity actually improved across both arms of the study. As described in the results: *"At the end of the study, 26/72 (36.1%) participants on sertraline felt appreciable improvement and 31/75 (41.3%) on placebo A minority felt sufficient benefit for long term use (sertraline 18.6%; placebo 26.3%)"*.

These observations highlight two clinically relevant points; first, the problem of demonstrating the superiority of a drug over placebo in a randomized placebo-

controlled trials (RCT) which is the gold standard for proof of efficacy and second that there is now increasing realisation about how placebo might be harnessed for clinical benefit.

Placebo responses are well-documented in many conditions including chronic pain, depression and asthma [2]. In RCTs placebo response is a well recognised factor that masks the true pharmacodynamic effects of a drug. This is a particular issue in early small-scale Phase II studies (proof of concept stage) where some evidence of efficacy is sought before the drug can be advanced to the next stages. Due to the placebo effect a drug with true pharmacodynamic effects might be dropped early in drug development [3].

Placebo response has a neural basis thought to be related to shaping the way the brain forms expectations [4]. Emerging evidence highlights the role of expectation in the way the brain generates the feelings of breathlessness [5,6]. It is possible that drugs acting in the central nervous system can interact with these networks when there is another central nervous system acting drug on board failing to mount the placebo related neural response in the drug arm [7]. This then challenges the validity of the whole premise of randomised controlled trials which assume that expectation driven aspects are equal in the drug arm and the placebo arm. Although expectation driven components might seem equal, the neural basis that drives the symptomatic improvement in both arms might not be the same in the placebo and the drug arm.

The second point it highlights is the importance of the potential benefits of placebo treatment that is often ignored by the medical professionals [8]. The term "placebo" is often used disparagingly to suggest a treatment does not work. Prescribing of placebo is restricted, due to ethical concerns about deception.

A recent upsurge in interest in harnessing placebo response for clinical benefit in the treatment of chronic pain has direct relevance for chronic breathlessness. Some of the ethical concerns have been addressed by the use of "open label" placebo, in which patients are fully aware that they are receiving an inert medicine [8]. The trials explain open label placebo in positive terms, such as "this pill has no active constituents but has been shown to work for some people". A recent systematic review on open label placebo in several clinical conditions indicate a significant beneficial effect when compared to no treatment though larger clinical trials are needed to this concept [9].

Based on the findings of Currow et al [1], combined with what's already known about placebo in chronic pain, we feel that this is a sufficient evidence base to support further research on the mechanisms of placebo in chronic breathlessness, the duration of the placebo response and also on the open label placebo concept.

References

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