Something fishy: The issue of omega-3 blinding in psychiatric clinical trials

Jean C Liu\textsuperscript{1,2}, Rebecca P Ang\textsuperscript{3} and Daniel S Fung\textsuperscript{1-3}

Introduction

In medical research, clinical trials evaluate drug efficacy, the ability of a pharmacological product to reduce or manage clinical symptoms. However, symptomatic improvements following drug delivery can arise from: the pharmacological action of the drug (drug effect), natural improvements over time (spontaneous recovery), and patient expectations associated with the psychological notion of receiving a treatment (placebo effect; Finniss et al., 2010; Price et al., 2008). Thus, assessments of drug efficacy need to partial out pharmacological contributions over and above spontaneous recovery and placebo effects.

Double-blinding in clinical trials

Spontaneous recovery can be accounted for by including a control group monitored for the same duration without receiving the active drug treatment. On the other hand, placebo effects are harder to control for: when patients desire a particular treatment outcome, believe they are receiving a certain form of treatment, or expect that the treatment will obtain a desired treatment outcome, this psychosocial context alone has been found to improve clinical symptoms (Finniss et al., 2010; Price et al., 2008). That is, even when patients receive a sham treatment that should not affect symptomology, if given within the right psychosocial context it can reduce patient symptoms. Further, with small or null drug effects, what the patient believes can account for a larger variance of the observed treatment effect than whether patients receive the real or sham treatment (e.g. Colagiuri et al., 2009).

Although the placebo effect has been reported for a range of medical conditions, it may be most relevant for psychiatric conditions or psychological phenomena (e.g. pain and phobia: Hunsley and Westmacott, 2007; depression: Rutherford et al., 2010). Consequently, clinical trials – particularly those involving emotions and behaviours – need to control for the placebo effect. The International Conference on Harmonisation (ICH, 2000) recommends a placebo-controlled design where participants receive either the study drug or a placebo, a substance identical to the study drug except without the active pharmacological component; the design should also be double-blinded, such that both participants and trial administrators do not know which experimental condition participants are allocated to.

Using a double-blind placebo-controlled design accounts for the placebo effect by matching the psychosocial context in both experimental conditions. Nonetheless, the onus remains on the researcher to provide evidence of double-blinding integrity; if shown successfully, then observed drug effects over and above that found with the placebo can be said to be true pharmacological effects. In this article, we examine double-blind methodologies in psychiatric trials for a nutritional intervention – omega-3 supplementation.

Theoretical discussion on omega-3 blinding

There is growing interest in how alternative medicine may complement standard medical treatments, and several researchers have focused on the role of omega-3 fatty acids in the prevention and management of psychopathology (Freeman et al., 2006; Politi et al., 2011). Omega-3 fatty acids are essential fatty acids in that they cannot be synthesized by the body and need to be consumed through dietary sources (e.g. fish). Several studies have linked inadequate concentrations with increased rates of psychiatric morbidity (Freeman et al., 2006), suggesting a possible role of supplementation to manage clinical symptoms. To evaluate clinical utility, trials of omega-3 supplements need to apply the same standards required of pharmaceutical trials (Werneke et al., 2006) – namely, by using double-blind placebo-controlled designs. We suggest that this has not always been
applied, and highlight four issues relevant to omega-3 supplementation that may pose a challenge to this design: participant expectations, timing of effects, taste, and self-administration (Table 1).

### Issues related to omega-3 blinding

#### Participant expectations

The first issue relates to expectations that participants may bring into a clinical trial. Omega-3 is easily accessible to the general public through dietary sources or through supplements sold off the counter. Market research suggests that this availability, coupled with extensive marketing, has resulted in public familiarity and expectations regarding omega-3: for example, Frost & Sullivan (2010) report that consumers perceive omega-3 supplements to be beneficial for overall health, preventing heart disease, promoting skin and hair health, and assisting with brain functioning. These expectations would likely heighten the placebo effect amongst participants who join a trial of omega-3. (It is also possible that participants could join the trial with pre-existing scepticism, as was reported in Patch et al., 2005; however, these participants likely form a minority because trial participation is voluntary.)

High omega-3 expectancy has two implications: first, if the pharmacological effects of omega-3 are small or null for a particular outcome measure, then relative to these pharmacological effects participants’ expectations may have a larger contribution on observed changes in the outcome. Second, if participants somehow become cognizant of what drug they are taking (i.e. the blinding is broken), those in the omega-3 condition will likely be influenced by positive omega-3 beliefs they may have (whereas those in the placebo condition would not be influenced by these beliefs). Thus, if blinding is broken, it is likely to favour omega-3, with participants’ pre-existing beliefs inflating any drug effect observed.

#### Timing of effects

A second factor influencing participant beliefs is how long it takes for omega-3 effects to be seen. Animal studies suggest that following omega-3 deficiency, supplementation for at least 8 weeks is required for brain composition of omega-3 to be restored (Moriguchi et al., 2001). Thus, depending on the mechanism of action, psychiatric trials of omega-3 may require a waiting period of weeks to months before behavioural changes can be observed. This accords with the preponderance of published omega-3 trials, where positive behavioural effects have been reported following a latency period of at least 4 weeks (Freeman et al., 2006; Politi et al., 2011; see also Gertsik et al., 2012 for a study tracking possible effects across time). If so, this is longer than in trials of several other psychiatric drugs, where drugs targeting a specific receptor can exert behavioural effects more rapidly (e.g. as is the case with anxiolytics; however, we note that drugs such as selective serotonin reuptake inhibitors are associated with similar waiting periods.) This lag time may have an influence on which drug participants believe they are taking: for example, during the lag time, participants may search for physiological or behavioural effects and attribute effects to omega-3 when these are not related to the pharmacological effect of the drug. Alternatively, participants may not observe any differences during this lag time and so believe they are taking the placebo (even if they were taking omega-3). Either way, if blinding is successful, these beliefs should be independent of the actual drug condition (with no systematic differences in group beliefs); however, as before, these beliefs can have a larger contribution to the outcome measures if the pharmacological omega-3 effect is null or small. It should also be noted that if the lag time results in many participants believing that they have taken the inactive placebo, this would not influence the pharmacological effect of omega-3 being observed (i.e. it should not affect group differences), but in reducing the psychosocial context may lead to an overall decrease in treatment magnitude being seen (across both omega-3 and placebo groups).

#### Taste

Apart from participants’ beliefs, the integrity of blinding itself could be compromised since most omega-3 supplements have a strong odour and fishy taste that are difficult to disguise. This is a genuine concern, with a

### Table 1. Handling challenges specific to clinical trials of omega-3

<table>
<thead>
<tr>
<th>Nature of challenge</th>
<th>Potential impact on conclusions made</th>
<th>Recommendations to address challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant expectations</td>
<td>Favours omega-3</td>
<td>Collect evidence of successful blinding</td>
</tr>
<tr>
<td>Timing of effects</td>
<td>Reduces overall responses found (regardless of group)</td>
<td>Collect evidence of successful blinding</td>
</tr>
<tr>
<td>Taste</td>
<td>Favours omega-3</td>
<td>Match placebo for taste and odour of omega-3 Collect evidence of successful blinding</td>
</tr>
<tr>
<td>Self-administration</td>
<td>Reduces or masks any true group differences</td>
<td>Validate actual omega-3 consumption (e.g. through food diaries, blood samples)</td>
</tr>
</tbody>
</table>
reviewer in two authors’ (RA and DF) grant application questioning if it would even be possible to blind participants successfully. Of note, in several published psychiatric trials (e.g., Gertsik et al., 2012; Grenyer et al., 2007), no apparent effort was made to match the placebo by taste: in these trials, the placebo was simply a different type of oil (e.g., safflower oil, olive oil), which would match the active omega-3 by texture but not have a similar fishy taste.

Difficulty in taste matching is compounded by omega-3 being widely consumed by the general public: as a consequence, some participants may recognize what omega-3 products taste like and be able to differentiate the active omega-3 from the placebo. As discussed earlier, if blinding is broken, placebo effects alone (from participants’ expectations) would likely favour omega-3.

Self-administration

Finally, omega-3 blinding could be compromised by self-administration of omega-3, regardless of randomization group. Standard clinical trials have protocols to control for participant use of non-study drugs, and non-compliant self-administration – as long as not selectively different between groups – may result in a larger error variance within each drug group but would not affect the primary manipulation itself. However, in the case of omega-3 clinical trials, the active component itself (omega-3) can be easily consumed through publicly available supplements or dietary choices. Motivation to self-supplement may also be heightened to the extent that participants expect benefits from omega-3, particularly if participants also believe that they were allocated to the placebo group or are somehow not receiving an optimal dosage of omega-3 (and hence supplement to avoid missing out on omega-3 benefits).

Should participants self-administer omega-3 supplements, then the experimental condition participants were randomised to would not represent participants’ actual state of omega-3 consumption. Such a situation would render the experimental manipulation ineffective, and a comparison of participants based on their allocated condition would be erroneous: if there were indeed a true effect of omega-3, this would likely be masked or diminished.

Recommendations for future studies

When unaddressed, these challenges limit confidence about omega-3 effects reported. Accordingly, we suggest recommendations for future trials of omega-3, and have begun to implement these in an ongoing trial on the effects of omega-3 in children with disruptive behaviour disorders.

Placebo choice

First, at the stage of experimental design, due consideration should be given to taste matching when choosing a placebo. For example, a nominal amount of omega-3 (at a much smaller dose than in the active condition) or a non-active fishery product could be added to the placebo to give it a fishy taste. This has been carried out in several clinical trials (e.g., Hallahan et al., 2007; Lesperance et al., 2011) and may reduce the risk of broken blinding through taste. Different modes of supplement delivery (e.g., capsules, gummies, liquid formula) could also contribute to participants’ ability to identify the supplements, and can be chosen accordingly.

Validation of actual consumption

At the stage of data collection, validation procedures are needed to ensure that participants’ actual omega-3 consumption differs according to the experimental condition they were allocated to. To control for possible dietary supplementation, researchers could seek to match the diet between the omega-3 and placebo groups; validation of actual omega-3 consumption should also be carried out by collecting food diaries and blood samples across the trial duration. If blood samples fail to differentiate experimental groups in terms of omega-3 levels, conclusions of omega-3 effects based on group-level statistics will simply not be valid; instead, participant groups could be
redefined based on blood levels of omega-3.

Evidence for blinding integrity

Finally, to increase confidence that positive omega-3 effects are not merely due to expectancies, there needs to be evidence that successful blinding has occurred. This is of grave importance if the placebo did not match the omega-3 supplement by taste, as the possibility of compromised blinding is real (as was reported by Grenyer et al., 2007); even if a placebo was chosen to have a fishy taste, blinding integrity still needs to be established as omega-3 participants may still report having a fishy after-taste more often than placebo participants (as was reported by Lesperance et al., 2011). Consequently, there needs to be evidence showing that omega-3 blinding is possible, and that it was successful in a particular clinical trial.

Trial-level evidence. One way in which evidence could be collected is, at the data collection stage, by asking participants: (i) which supplement they think they received (omega-3 or placebo), (ii) how confident they are of this, (iii) their reasons for this belief, (iv) whether they have noticed effects of the supplement, and (v) their expectancies as to what this supplement should do. These guidelines were drawn from research addressing the placebo effect (Colagiuri et al., 2009; Price et al., 2008), and allow subsequent statistical and qualitative analyses on whether drug expectancy causes or mediates the drug outcomes reported. We suggest, at a minimum, that publications report whether there is a systematic relation between actual and believed group allocation. (To date, there have only been a handful of omega-3 studies that have done so; e.g. Grenyer et al., 2007; Lesperance et al., 2011.)

We further suggest, in line with guidelines for clinical trials in general, that these data should be sought at the start rather than end of the trial; this is because effective treatment resulting from the pharmacological action of the drug can result in participants correctly identifying which drug they received by the end of the trial (Sackett, 2004). (In so recommending, we note a potential concern that the mere asking of participants could modulate their expectancies about the drug for the remainder of the trial. However, we highlight that this should not systematically affect one drug group more than the other, and thereby should not affect the comparison made between the two drug conditions).

Avenues for future research. Finally, we suggest that beyond a single clinical trial, blinding integrity in omega-3 trials can be promoted by explicit research on whether participants can tell the difference between omega-3 and placebo supplements, and which factors may contribute to their ability to so differentiate (e.g. by manipulating the nature of the placebo or the mode of supplement delivery). This will assist in design decisions for future trials of omega-3, and allow greater confidence in conclusions made about how omega-3 may affect psychiatric conditions.

Conclusion

In conclusion, we highlight the need for omega-3 clinical trials to adhere to the rigorous standards required of pharmaceutical clinical trials – those of a double-blind placebo-controlled design. We suggest four aspects that could challenge this design (participant expectations, timing of effects, taste, and self-administration) - that, as a result, may diminish confidence in conclusions made about omega-3. Accordingly, we emphasize the need for future trials to address these concerns through: careful placebo choice, validation of actual omega-3 consumption, and by providing evidence that blinding can be and has been successful.

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Declaration of interest

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