

NEURAPRO-Q Study: Objection to trial on ethical and methodological grounds

We wish to register our objection to the proposed NEURAPRO-Q trial, details of which are given below:

Melbourne Health trial number	2010.041
ACTR number	ACTRN12610000244000
Australian New Zealand Clinical Trials Registry (ANZCTR) registration title	The NEURAPRO-Q (North America, EUROpe, Australia PROdrome) Study: A multicentre randomised controlled trial (RCT) to evaluate the effect of Quetiapine and Cognitive-Behavioural Case Management on the incidence of first episode psychosis in Symptomatic Patients at Ultra-High Risk for Early Progression to Schizophrenia and Other Psychotic Disorders
Public title	A comparison study of quetiapine medication and psychological therapy versus placebo tablets and psychological therapy in patients who are deemed at risk of developing a psychotic disorder
Trial acronym	NEURAPRO-Q
ANZCTR URL	http://www.anzctr.org.au/trial_view.aspx?id=335264

The ethical guidelines of the National Health and Medical Research Council emphasise the importance of setting an appropriate balance between potential risks and benefits in the conduct of clinical trials.¹ The literature on the study of individuals at 'high risk' of transition to psychosis has highlighted some of the difficult ethical problems associated with this research. There is still no consensus that such research, let alone treatment, can be justified while the rate of conversion to psychosis remains low, but the risks of harm to trial participants and patients who are 'false positive' for future psychosis are considerable. This is particularly the case when full therapeutic doses of antipsychotic medications may be prescribed (as in this proposed trial), with the attendant adverse effects.

There are four important ethical issues raised by this proposed trial:

1. The ethics of causing unnecessary harm to individuals not requiring treatment, in order to possibly prevent harm to a smaller number who do require treatment.
2. The ethics of risking harm to research participants when the above consideration would preclude the use of this treatment, even if it proved effective, in clinical practice in the absence of a clear predictive marker for future psychosis.
3. The ethics of risking harm to participants when the flaws in the proposed methodology mean that the trial will not establish any truly preventive effects of the treatment – the stated purpose of the trial.
4. The ethical conflict of interest involved in choosing this particular drug, for a trial funded by its manufacturer, when this company (along with other antipsychotic manufacturers) has a track record of serious ethical breaches involving 'off-label' marketing, misuse and suppression of research trial data, recruiting 'key opinion leaders' to promote antipsychotics as 'broad spectrum' psychotropics, and so on.

Specific points in relation to these issues are addressed below.

1. Lack of an accurate marker for future psychosis, and very high false positive rate

Ethical concerns surrounding the identification of an 'at risk' state for psychosis are long-standing.^{2,3} Two major risks are the stigmatisation/labelling of those identified as being at risk of progression to psychosis, and the inducement of unnecessary anxiety about those risks. However, an even more serious risk is unnecessary pre-emptive use of antipsychotic medication, with potentially serious side-effects. The central ethical issue is whether it is justified to cause unnecessary harm to those who are not destined to progress to psychosis, in order to prevent or reduce harm to those who are. The current consensus is that without an accurate predictive marker for psychosis, the use of potentially harmful interventions to prevent psychosis cannot be justified. For example, Klosterkötter⁴ suggested that a false-positive rate of 10% or less would be needed to justify any preventive intervention that had harmful side-effects.

Professor McGorry has recently argued that early intervention is justified at a false positive rate of 80% within a defined high-risk group, given that this represents 200 times the general population risk.⁵ However, he specifically ruled out the use of pharmacological interventions in this high-risk group, acknowledging that such interventions need to be safer and more effective than those used after the onset of frank psychosis. Indeed, he stated that even after the first episode, low doses of antipsychotics are to be preferred.

Despite these assertions, Professor McGorry continues to research the use of antipsychotics (including high doses) in individuals as young as fifteen who are at risk for psychosis, as in this trial (NEURAPRO-Q). Such an approach might be justified if there were reliable markers for psychotic disorders, and if a genuine prodrome (as opposed to an at-risk state) had commenced. Currently, there are no reliable genetic markers for schizophrenia,⁶ nor is there any realistic prospect of any. The false-positive rate in high-risk groups using other markers⁷ has not yet dropped to anywhere near the 10% false-positive rate suggested by Klosterkötter to provide ethical justification for such an intervention.

2. Ineffectiveness of antipsychotics in previous trials

The results of previous trials of antipsychotics as treatment for people at high risk of psychosis have been unpromising. The recently released updated Cochrane review of early intervention for psychosis⁸ identified only two methodologically acceptable trials. In McGorry et al.'s PACE (Personal Assessment and Crisis Evaluation) trial, a significant difference in transition between placebo and risperidone groups was found at six months but not at 12 months.⁹ These results are consistent with a predictable *masking* of the onset of psychosis, not with *prevention* of that onset.

In McGlashan et al.'s PRIME (Prevention Through Risk Identification, Management, and Education) study, conversion rates did not differ significantly between patients treated with olanzapine and patients treated with placebo, in either the treatment year or the follow-up year.¹⁰ Similarly, the North American Prodrome Longitudinal Sample found no significant association between atypical antipsychotics and conversion to psychosis.¹¹

3. Promising results of 'fish-oil' (omega-3 fatty acids) trial

In contrast to the unpromising results with antipsychotics, there is stronger evidence for the effectiveness of long-chain omega-3 polyunsaturated fatty acids, which are highly concentrated in fish oil. Professor McGorry was a co-investigator in Amminger et al.'s Austrian randomised controlled trial of omega-3 fatty acids in fish-oil capsules for subthreshold psychosis.¹² Compared with placebo (coconut oil), fish oil resulted in significantly lower rates of transition to psychosis, significantly reduced positive and negative symptoms, and improved functioning (all after 12 months). The incidence of adverse effects did not differ significantly between the two groups, and fish oil is known to be safe. The rate of transition to psychosis was lower than in the above trials of antipsychotic medication.

4. Harms caused by atypical antipsychotics

The substantial harms caused by quetiapine and other atypical antipsychotics include weight gain (a mean of 8.79 kilograms in McGlashan et al.'s PRIME trial), diabetes, metabolic syndrome and neurological symptoms, and these drugs carry the risk of brain shrinkage¹³ (contrary to the 'potential neuroprotective effects' mentioned in secondary outcome 3) and premature mortality. Many of these adverse events are long-term outcomes. While weight gain will emerge within 6 months,¹⁴ this very short timeframe is not long enough for the more significant adverse effects to peak. The protocol allows exposure to high doses (400 mg) of quetiapine, further compounding the risk.

5. Short timeframe of NEURAPRO-Q trial

We have already commented that the six-month timeframe of the study is too short for some of the potential adverse effects to emerge and/or peak. Furthermore, this timeframe is too short to adequately assess the primary outcome, incidence of first episode psychosis, which can take years to emerge – Klosterkötter et al. reported a mean prodromal duration of 5.6 years.¹⁵ The NEURAPRO-Q study group would be well aware of this; Professor McGorry led the PACE trial which found a significant difference in transition between placebo and risperidone groups at six months but not 12 months.¹⁶

6. Suppression of symptoms of primary outcome

The primary outcome is 'the incidence of first episode psychosis in an Ultra High Risk (UHR) group'.¹⁷ But if we accept the current evidence that quetiapine reduces psychotic symptoms, then the scale used to detect the onset of psychosis in this study – the Comprehensive Assessment of At Risk Mental States (CAARMS) – would not be expected to detect many cases of emergent psychosis in the quetiapine group, since that condition will already be being 'treated' by potentially full therapeutic doses of quetiapine throughout the six months of the trial. Thus, it is symptom suppression rather than transition to psychosis that will be measured. This will strongly bias the results in favour of quetiapine over placebo. It also means that this is not a trial of prevention, as claimed in the trial protocol, but a trial of the absolute (not relative) effectiveness of quetiapine as an antipsychotic. Since quetiapine has known antipsychotic properties, but is no more (and sometimes less) effective than other

antipsychotics, the trial has no scientific value that would justify the risks to the participants.

7. Use of NEURAPRO-Q trial as a marketing strategy

Of more concern is secondary outcome 1 ('To investigate the effects of quetiapine, in addition to CBCM, on clinical status and the level of symptoms and functioning in the UHR group'), which seems aimed at creating a role for quetiapine as a 'general purpose' or 'broad spectrum' psychotropic, a role promoted by Professor McGorry.¹⁸ Again the dampening of symptomatology might be used to justify the use of this medication, even when that symptomatology is not sufficient (by definition) to justify the diagnosis of psychosis. The timeframe of the study is such that any 'positive' results in terms of dampening symptoms will emerge within the timeframe, whereas many serious adverse effects will not have emerged. When these findings are reported, this will potentially lead to widespread use of quetiapine in this 'general purpose' way for a range of symptoms (including depression), at potentially significant cost in terms of morbidity and mortality. There is ample evidence of atypical antipsychotics being widely used beyond their approved indications despite warnings of their risks.¹⁹

In this context, the previous unethical behaviour of AstraZeneca, and their competitors, in promoting the prescription of antipsychotic medications 'off label' (including promotion as "'broad spectrum psychotropics" that purportedly work to alleviate a wide variety of symptoms"²⁰) is highly relevant. Recently, AstraZeneca paid US\$540 million to settle two lawsuits with the United States government relating to the sale and marketing of Seroquel® (quetiapine), including off-label marketing of the drug for unapproved uses (attachment A).²¹ There are 14,444 civil lawsuits outstanding regarding serious side-effects such as diabetes attributed to misleading marketing of the drug. This followed a payment of US\$1.42 billion by AstraZeneca's competitor Eli Lilly to settle civil and criminal suits regarding the antipsychotic Zyprexa® (olanzapine) (attachment B).²² The company Janssen is currently under investigation over similar marketing of the antipsychotic Risperdal® (risperidone) (attachment C).²³

These cases led to the release of internal company documents that revealed the extent of ethical breaches, in particular the use of clinical trials for marketing purposes. Rather than reiterate that evidence here, we provide a full version of an article by Glen Spielmans and Peter Parry recently published in the journal *Bioethical Inquiry* (attachment D).²⁴ We draw particular attention to the section 'Suppressing and Spinning Negative Data', which describes how AstraZeneca suppressed clinical trial data that would be unhelpful for the marketing of quetiapine. In addition, the section 'Investigator-initiated Trials and Opinion Leaders' shows how the company recruited supposedly independent investigators of high standing to give greater credence to clinical trials of quetiapine. It is difficult to think of a more prominent opinion leader in Australian psychiatry than Professor McGorry, the listed spokesman for this trial.

8. Misleading statements describing the trial

According to the brief summary section of the trial description, there is evidence that treatment of at-risk people is *likely* to be beneficial:

Previous research indicates that psychological and pharmacological intervention is likely to benefit patients who are Ultra High Risk of developing psychosis. If treatment is initiated as soon as possible after the onset of sustained positive psychotic symptoms, many damaging psychosocial consequences may be delayed or prevented, and symptoms reduced.

However, this claim is not supported by the Cochrane review of early intervention for psychosis. The 2006 review,²⁵ which was current at the time of the trial description, identified only two methodologically acceptable trials of treatment of people at risk of developing psychosis, and reported unpromising results:

One small Australian trial (n=59) was concerned with a phase-specific intervention (low dose risperidone and cognitive behavioural therapy) for people with prodromal symptoms. This group were significantly less likely to develop psychosis at a six month follow up than people who only received care from a specialised team which did not involve phase-specific treatment (n=59, RR 0.27 CI 0.1 to 0.9, NNT 4 CI 2 to 20). This effect was not significant at 12 month follow up (n=59, 1 RCT, RR 0.54 CI 0.2 to 1.3). A UK-based study (EDIE) randomised 60 people with prodromal symptoms, to cognitive behavioural therapy (CBT) or a monitoring group. Only two outcomes were reported: leaving the study early and transition to psychosis, both sets of data were non-significant. (p. 1)

The 2011 updated review²⁶ identified six studies, only one of which (Amminger et al.'s omega-3 fatty acid fish-oil study) was promising:

For the six studies addressing prevention of psychosis for people with prodromal symptoms, olanzapine seemed of little benefit (n=60, 1 RCT, RR conversion to psychosis 0.58 CI 0.3 to 1.2), and cognitive behavioural therapy (CBT) equally so (n=60, 1 RCT, RR conversion to psychosis 0.50 CI 0.2 to 1.7). A risperidone plus CBT plus specialised team did have benefit over specialist team alone at six months (n=59, 1 RCT, RR conversion to psychosis 0.27 CI 0.1 to 0.9, NNT 4 CI 2 to 20), but this was not seen by 12 months (n=59, 1 RCT, RR 0.54 CI 0.2 to 1.3). Omega 3 fatty acids (EPA) had advantage over placebo (n=76, 1 RCT, RR transition to psychosis 0.13 CI 0.02 to 1.0, NNT 6 CI 5 to 96). We know of no replications of this finding. (p. 2)

Thus the brief summary presents a very biased interpretation of the evidence about treatment of people at risk of developing psychosis as justification for this poorly designed trial.

Furthermore the second sentence in the above quote from the brief summary section of the trial description misleadingly refers to '*sustained* positive psychotic symptoms' [italics added], despite the fact that *none* of the three ultra-high-risk groups specified in the inclusion criteria is defined by *sustained* positive psychotic symptoms. The three groups are:

Vulnerability (Trait and State Risk Factor) Group: Individuals with a combination of a trait risk factor (schizotypal personality disorder or a family history of psychotic disorder in a first degree relative) and a significant

deterioration in mental state and/or functioning or sustained low functioning during the past year.

Attenuated Psychotic Symptoms (APS) Group: Individuals with *subthreshold* (intensity or frequency) positive psychotic symptoms. The symptoms must have been *present during the past year* and be associated with a significant reduction in or sustained low functioning.

Brief Limited Intermittent Psychotic Symptoms Group (BLIPS): Individuals with a recent history of frank psychotic symptoms that *resolved spontaneously* (without antipsychotic medication) within one week. The symptoms must have been *present during the past year* and be associated with a significant reduction in or sustained low functioning. [italics added]

The Vulnerability Group need never have had *any* psychotic symptoms, the Attenuated Psychotic Symptoms Group need only have had *subthreshold* symptoms *at some point in the previous year*, and the Brief Limited Intermittent Psychotic Symptoms Group is defined by psychotic symptoms that *lasted less than a week and resolved spontaneously*.

This misrepresentation of the clinical state of the participants, combined with the emotive reference to 'many damaging psychosocial consequences', exaggerates the need for treatment, complementing the exaggeration of the benefits of treatment.

Summary

In summary, the NEURAPRO-Q trial will use the atypical antipsychotic quetiapine, which has well documented harms, for 'treatment' of people at high risk of psychosis, despite evidence of the ineffectiveness of antipsychotics for this purpose (misrepresented in the trial description), and despite much more promising evidence for a safer alternative treatment, omega-3 fatty acids. Furthermore, in the absence of a predictive marker for psychosis, the high false positive rate means that most of the people treated with quetiapine would not have become psychotic in the absence of treatment. Not only is the use of atypical antipsychotics such as quetiapine potentially dangerous, it is also costly, and its use is at the expense of other interventions that on the current evidence are both safer and more effective.

In addition, the timeframe of the trial is too short to adequately assess the primary outcome, incidence of first episode psychosis, and too short for some of the adverse effects to emerge and/or peak. Furthermore, because quetiapine suppresses symptoms of psychosis, and it will be administered throughout the six-month trial, the trial will not be able to detect the emergence of many cases of emergent psychosis in the quetiapine group, which will strongly bias the results in favour of quetiapine. There is a strongly arguable case that this poorly designed trial represents a valuable marketing strategy for AstraZeneca, the manufacturer of quetiapine and the sponsor of the trial. We note that AstraZeneca has not provided support for a comparative study of essential fatty acids (the NEURAPRO-E trial). There is a danger that this short-duration trial may be used to justify the prescription of quetiapine to individuals who are not psychotic, for more extended periods, with the risk of serious harms such as weight gain and diabetes. This cannot be justified when there is evidence that safer and more effective treatments may be available. The main benefit would accrue to AstraZeneca in expanding the market for their drug; the harms would be borne not

only by trial participants, but also by a much larger number of people prescribed quetiapine for a broad spectrum of symptoms.

On the basis of these serious ethical and methodological problems, we request that the NEURAPRO-Q trial be denied ethical approval. The claimed benefits do not stand up to analysis, but the risks are considerable. Therefore, the trial does not meet the NHMRC ethical guidelines in relation to an appropriate balance between potential risks and benefits and it should not proceed.

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