Author’s response to reviews

Title: The Efficacy of Sodium Benzoate as an Adjunctive Treatment in Early Psychosis - CADENCE-BZ: study protocol for a randomized controlled study

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Reviewer’s comments

Q1. More clearly define the operational definitions of early psychosis and alternative medical treatment and justify why focusing this illness subgroup in term so onset of illness and its treatment.

Answer Q1.

The definition of early psychosis is in keeping with the widely used standards for this field of research. Participants must have had their first onset of this diagnosis within the last two years. This is outlined in the ‘Inclusion Criteria’ section (page 9, 2nd paragraphs). We have chosen this broad spectrum psychosis group (schizophrenia, schizophreniform psychosis, delusional disorder, bipolar disorder, psychosis not otherwise specified) with an expectation that sodium benzoate will be effective in treating these groups of patients as there is evidence that sodium benzoate has been effective in treating schizophrenia (Lane et al. 2013).

We have adjusted the text to alert the general reader of this definition (page 9, 2nd paragraphs)

Q2. The evidence on the use and effect of sodium benzoate and related alternative medications/supplements should be further strengthened.

Answer Q2

This is outlined in Section “Rationale for use of sodium benzoate for the treatment of schizophrenia”. We have added texts reflecting use and effect of sodium benzoate for other mental disorders in clinical trial settings (page 5-6, 4 paragraphs). The evidence of the effect of sodium benzoate has been shown by a recent publication by Lane et al. 2013. In addition, the biological mechanism linking psychosis with the N-methyl-D-aspartate (NMDA) neurotransmitter system has been outlined in the previous section, “Novel interventions for psychosis”.

Q3. “The current acceptable daily intake of sodium benzoate is 0.5 mg/kg body weight as suggested by the joint committee by the Food and Agriculture Organization of the United Nations and the World Health Organization [15]. It is noted that intake estimations from several counties gave averaged 0.18-2.3mg/kg body weight…” In addition, “The therapeutic dose administered to treat hyperammonaemia over several years is in the range of 250-500 mg/kg body weight per day…” Now, your treatment dosage is planned to be “determine if 12 week treatment of 1000mg (500mg BD) Sodium Benzoate treatment”.

Answer Q3
The summary of our text is correct. We have chosen the same dose of sodium benzoate as used in the previously published RCT of sodium benzoate (Lane et al 2013). The other doses relate to the use of this compound as a food preservative, not as a treatment for schizophrenia/psychoses.

We have re-arranged and added relevant texts in order to highlight the rationale of the dose used in this study (pages 5 -6, ‘Rationale for use of sodium benzoate for the treatment of schizophrenia’ section, and page 11 ‘Dose justification’ section).

Q4. Any anti-psychotics or other psychotropic drugs to be taken during the study period and if yes, any interactive or confounding effects of the current medications with the drugs being tested?

Answer Q4

This is an augmentation study (note we have used the word ‘adjunctive’ in the title of the protocol), thus we expect that most if not all of the patients will be provided with standard antipsychotic treatments. There is no evidence of adverse drug interactions between sodium benzoate and antipsychotics, while there is evidence that the addition of this compound to antipsychotic drugs is beneficial (thus, the scientific rational for the current protocol) (Lane et al 2013).

Q5. How to determine the optimal dose of the medication used? Why using your treatment dose of standardised 1000mg per day even though there are individual variations of medication dosage (e.g., between 250 – 1000mg daily by Lane et al.) for therapeutic use?

Answer Q5

We have used the same dose of 1000mg in this study as used by Lane et al. (2013). This has been detailed in “Dose justification” section (page 11).

Lane et al mentioned an earlier open-label pilot study that used varying doses of sodium benzoate between 250 and 1000 mg/d. That pilot study was a dose finding trial performed by dosing three of 5 patients received 1000 mg/d of benzoate, in which their PANSS total scores decreased from 78 to 58, 80 to 59, and 84 to 60, respectively (i.e. significant improvement). The other 2 patients received lower dosages and did not improve.

Q6. Considering adherence and compliance for analysis? How? How to check the adherence?

Answer Q6
We have added text that describes compliance monitoring and adherence as well as the accountability of the study medications (pages 14 & 15, ‘Compliance monitoring and adherence’ section). We acknowledge that this is an important omission.

Other than regular telephone contacts, at each visit the participants are asked about compliance and also asked to hand back remaining study medication. This is counted and recorded in the ‘care-report from’ as well as in the ‘investigational product dispensing log form’.

Q7. Allocation sequence and procedure: Considering inter-cluster (5 clusters) correlations in sampling and data analysis?

Answer Q7

We do not plan to undertake any inter-cluster analyses with this study. The 5 recruitment sites are comparable and we have no prior hypothesis related to between-site differences. The stratification by site was included in order to provide balanced treatment allocation within each sites, as we predicted that some sites would be more efficient at recruiting participants than others.

Q8. Unclear meaning about the sentence (on p. 5): “... the distribution of the study medication will be supervised by an independent research pharmacist.”

Answer Q8

Details of the distribution of study medication are given in “Drug administration’ section (page 10) as follows:

“A delegated Research Pharmacist will dispense medication for all sites. For each randomised participant, the entire 12 weeks of study medication will be provided to QCMHR delegated research staff. The study medication will then be distributed to the participant on a fortnightly basis by delegated research staff. There will be a total of 7 dispensations per participant”.

We have also added new text to further clarify this issue:

“1000mg (500mg BD with meals-reminder aid) of sodium benzoate capsules will be used for the ‘intervention’ group while identical-appearing microcrystalline cellulose gelatine capsules will be used for the ‘placebo’ group in the study”.

Q9. Subject criteria: Why still using old version of DSM-IV criteria but not DSM-IV-TR or DSM-V?
Answer Q9

We are using the widely used Diagnostic Interview for Psychosis, which is a multi-diagnostic instrument that includes output for DSM IV. The diagnostic criteria for the disorders of interest to our study have been relatively stable across recent editions of DSM. We do not consider this issue a concern for our study.

Q10. Why focusing on those onset of a psychotic disorder within the last two years only?

Answer Q10

This is the widely used definition of ‘early psychosis’. Many studies focus on this period as it is believed that long term outcomes may be differentially influenced by treatment during this period. We have added new text to clarify this issue (page 6, 2nd paragraph):

“In recent decades there has been considerable attention to optimizing treatments during the first few years of onset [17,18]. Often described as ‘Early Psychosis’, this field of research believes that assertive treatments soon after onset may have better outcomes, compared to the same treatments when given to individuals with longstanding, chronic psychotic disorders. To date, we are not aware of studies that have examined the efficacy of sodium benzoate as a treatment of those with early psychosis. In our study, we will include patients with the onset of psychotic disorders within two years”.

Q11. How the current use of “antipsychotic medications for a period of at least one continuous month within the above two-year period” expected to associate with your results?

Answer Q11

We do not feel it is ethical to include patients into this study who have not had standard treatment with antipsychotic medication as per clinical practice guidelines. We believe that the use of this inclusion criteria will make our study more representative of the patients assessed in early psychosis services.

Q12. Why only those with a Positive and Negative Syndrome Scale (PANSS) total score of at least 55?

Answer Q12

This is a frequent inclusion criterion for psychosis studies – it excludes patients who have made a full recovery (and thus would not be expected to show any additional benefits from add-on
treatments). We have added additional text and relevant references related to this issue (page 9 ‘Inclusion criteria’ section).

“(5) Have a Positive and Negative Syndrome Scale (PANSS) total score of at least 55 (i.e. those who have at least moderate symptoms) [29,30]”

Q13. For exclusion criteria, not clear why or how “Comorbid physical illnesses that would impair the participants’ ability to complete the trial”? All of these needed to be clarified.

Answer Q13

This is a criterion that excludes patients with additional general medical disorders that hinder participation in the study. It is not feasible to pre-specify the entire set of possible conditions, but we expect the clinicians will use their judgement about this matter. It is a standard criteria in clinical trials in early psychosis. We have added text to assist the reader unfamiliar with this criterion.

Q14. Sample size: unclear about the calculation by using the effect can “detect a difference in mean PANSS Total of at least 7 units” any support for such difference in mean totals and what will be the expected SD? Q15. How is this related to your cited reference by Lane et al.’s study and their effect size?

Answer Q14-15

As a novel treatment, there is a lack of information about the expected effect size in this particular population (the Lane et al study was in chronic schizophrenia). The Lane et al study found a PANSS total difference of 9.7 units with a standard deviation of 14.3 (treatment group) with 6 weeks of intervention. The pilot study (cited in Lane et al paper) with 3 samples found an average difference of 18.6 units. Because our sample is selected from an early psychosis group we predict a slightly lower effect size, we estimate that the difference of 7 units on the PANSS total would be clinically meaningful. If we could use difference of 9.7 units with the similar variance and power (as used in Lane et al), we would need only a half of the sample size (n=83 with 15% attrition rate).

Q16. Any reference for the attrition rate expected?

Answer Q16
It is difficult to accurately predict attrition rate in RCTs, however based on our experience in Brisbane, and the experience of our colleagues working in comparable studies elsewhere in Australia, we believe that 15% is an appropriate attrition proportion.

Q17. How to ensure the control group are using anti-psychotics during the study and any medication changes to be monitored and taken consideration in the analysis?

Answer Q17

The study is a double blind study and thus we will not be able to identify ‘control’ patients. All participants will be monitored for study medication compliance. As there is no evidence of adverse drug interactions between sodium benzoate and antipsychotics, we expect that there would not be any major differences between treatment and placebo groups with any differential changes in antipsychotics use by the groups.

We do not plan to reanalyse the data with respect to background medication as we used the randomization to distribute these sources of variation between the two groups. We have no prior hypotheses related to differential impact of the study medication when used in combination with particular types of antipsychotic medications (also see Answer Q22).

Q18. More should be taken for adverse events reporting and appropriate measures to manage any of these events to ensure safety

Answer Q18

Each AEs and SAEs will be recorded in detail (page 14). We have adequate measures of reporting and management of AEs in the study. We have added the following texts for reporting and appropriate measures to manage AEs/SAEs to ensure safety of the participants (page 16).

“We have developed a separate database about AEs reporting. We are using the MEDRA (Medical Dictionary for Regulatory Activities) coding system that includes System Organ Class (SOC), and following disease symptoms (LLT: Lowest Level Term) into the database for detailed record keeping of all related (and unrelated) AEs/SAEs. Each AE will be monitored until resolution or to the end of the 12 week protocol”.

Q19. Data analysis: whether Chi-square test used for categorical data of demographics?

Answer Q19.
We will be using chi-square test and/or Fisher exact test) whichever applicable based on the distribution of the variables. We have changed text reflecting these tests in the “Statistical analysis’ section (page 18).

Q20. How much missing data are expected? Why choosing ‘carry forward their last observation’ for filling in the missing data?

Answer Q20.

It is not unusual for data on some variables to be missing in community-based, pragmatic trails. For the current study, we are interested in the outcome measures, and for the ‘intention to treat’ analysis, we will carry forward the last observation in the standard fashion.

Q21. Any subgroup analysis or inter-cluster analysis? Any contrast or post hoc comparisons?

Answer Q21.

We are not planning any additional analyses (see also Answer for Q7).

Q22. Medications and their changes in the study and other changes in physiological condition or treatments may be considered for co-variance effect.

Answer Q22

We expect that background medication and psychological treatments will vary between patients and within patients (across the period of 12 weeks) (also see Answer Q17). We wish to make this study a pragmatic one with no plan for post-hoc analyses with respect to background medication as we will be using the randomization to distribute these sources of variation between the two groups. We have no prior hypotheses related to differential impact of the study medication when used in combination with particular types of antipsychotic medications.

Q23. Any limitations expected? for instance, this study may not able to determine the optimal dose for optimal effect of the treatment for individual cases of psychosis.

Answer Q23.

This is a phase III trial, not a dose finding study – we have added text to remind the reader that this will be an issue for future studies (page 20 ‘Discussion’ section).
“We have based the dose of sodium benzoate (1000 mg/day) on the most recent clinical trial (Lane et al 2013). However, it is feasible that alternative dosages may be optimal. Our study will not be able to explore this issue”.