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ORIGINAL ARTICLE

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# An open label pilot trial of low-dose lithium for young people at ultra-high risk for psychosis

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## Abstract

**Aim:** Lithium, even at low doses, appears to offer neuroprotection against a wide variety of insults. In this controlled pilot, we examined the safety (i.e., side-effect profile) of lithium in a sample of young people identified at ultra-high risk (UHR) for psychosis. The secondary aim was to explore whether lithium provided a signal of clinical efficacy in reducing transition to psychosis compared with treatment as usual (TAU).

**Methods:** Young people attending the PACE clinic at Orygen, Melbourne, were prescribed a fixed dose (450 mg) of lithium ($n = 25$) or received TAU ($n = 78$). The primary outcome examined side-effects, with transition to psychosis, functioning and measures of psychopathology assessed as secondary outcomes.

**Results:** Participants in both groups were functionally compromised (lithium group GAF = 56.6; monitoring group GAF = 56.9). Side-effect assessment indicated that lithium was well-tolerated. 64% ($n = 16$) of participants in the lithium group were lithium-adherent to week 12. Few cases transitioned to psychosis across the study period; lithium group 4% ($n = 1$); monitoring group 7.7% ($n = 6$). There was no difference in time to transition to psychosis between the groups. No group differences were observed in other functioning and symptom domains, although all outcomes improved over time.

**Conclusions:** With a side-effect profile either comparable to, or better than UHR antipsychotic trials, lithium might be explored for further research with UHR young people. A definitive larger trial is needed to determine the efficacy of lithium in this cohort.

KEYWORDS
lithium, psychosis, ultra-high-risk, UHR, young people

## 1 | INTRODUCTION

Individuals meeting the ultra-high risk (UHR) criteria are at high risk of developing a psychotic disorder. This group is therefore a prime target for indicated prevention to prevent a first episode of psychosis as well as for treatment of existing symptoms and disability (McGorry et al., 2018; Yung et al., 2003). A number of meta-analyses have indicated that specific intervention in young people identified as being at high risk of psychosis can reduce the risk of transition to psychotic disorder by up to 50%, although it remains unclear what the most effective type of intervention is (Davies, Cipriani, et al., 2018; Davies, Radua, et al., 2018; Mei et al., 2021; Stafford et al., 2013; van der Gaag et al., 2013). The use of antipsychotic medications for UHR or prodromal phase patients has been contested, since these medications carry the risk of negative consequences (i.e., side-effects) for potentially little benefit (Berger et al., 2007; Cornblatt et al., 2001; Warner, 2001). Alternative medications with fewer and less severe side-effects therefore warrant investigation.

Increasing evidence suggests that an active biological process occurs during the peri-onset phase of psychotic disorders (Gifford et al., 2017; Keshavan et al., 2005; Pantelis et al., 2003; Pantelis et al., 2005), raising the question of whether neuroprotective strategies may be efficacious in delaying or even preventing the onset of psychosis (Amminger et al., 2017). There is evidence that agents such as lithium have neuroprotective properties (Malhi & Outhred, 2016; Manji et al., 1999; Manji, Moore & Chen, 2000; Manji, Moore, Rajkowska et al., 2000; Moore, Bebchuk, Hasanat, et al., 2000; Moore, Bebchuk, Wilds, et al., 2000) and therefore might be ideally suited to this phase of psychotic disorder. Furthermore, a recent meta-analysis found that low doses of lithium (ranging from 200 to 1200 mg per day) are associated with a consistently positive safety profile (i.e., a low rate of adverse events; Strawbridge et al., 2023). Using such agents at this stage of disorder is consistent with the clinical staging model (Hartmann et al., 2018; McGorry et al., 2014), which proposes that intervention strategies need to be tailored to the stage of disorder.

Longitudinal imaging studies, from the UHR state for psychosis onwards, support the view that a dynamic process is associated with the transition to full-threshold psychosis (Kempton & McGuire, 2015; Pantelis et al., 2003; Pantelis et al., 2005). The underlying molecular process associated with this transition to full threshold psychosis is not clear; however, one possible explanation may be increased apoptotic activity (probably mainly of synaptic glial cells) in the pre- and peri-onset phase to the full-blown psychotic state (Berger et al., 2003; Jarskog et al., 2005; Morén et al., 2022). Indirect evidence that the onset of psychosis may indeed be associated with increased apoptotic activity comes from in vivo phosphorus magnetic resonance spectroscopy in drug-naïve individuals experiencing a first episode of schizophrenia showing increased membrane turnover (Berger et al., 2003; Keshavan et al., 1994).

The original intention of this study was to conduct an efficacy trial of low-dose lithium. However, competing demands to recruit to concurrent studies meant that the sample size recruited was far below that which would be required to test treatment efficacy. We therefore shifted the primary aim of this pilot study to test the safety of low-dose lithium (as indicated by side-effect data) in young people meeting the UHR criteria. This reformulation of the study as a Phase I trial was appropriate given that this pharmacological treatment had not previously been trialled in this clinical population. Secondary aims were to investigate whether the lithium-treated group would show (1) a lower rate of transition to psychotic disorder and (2) greater symptomatic and functional improvement compared WITH treatment as usual (TAU).

## 2 | METHOD

### 2.1 | Setting and design

This was a single site open-label non-randomized study of low-dose lithium. The neuroimaging data from this study have previously been reported in Berger et al. (2012). The study was conducted between 2000 and 2006 at the Personal Assessment and Crisis Evaluation (PACE) Clinic, a clinical service for young people at UHR of developing a psychotic disorder (Yung, 2007; Yung et al., 2007).

### 2.2 | Participants

Intake criteria for the study were: (a) being aged 14–30 years, (b) residing in the Orygen Youth Health catchment area, (c) persistent low functioning for at least 1 month or a significant drop in functioning within the previous 12 months and (d) meeting at least one of the following criteria for UHR status. (1) Attenuated psychotic symptoms (APS): presence of attenuated (subthreshold) positive psychotic symptoms within the previous 12 months. (2) Brief limited intermittent psychotic symptoms (BLIPS): history of brief self-limited psychotic symptoms, which spontaneously resolved within the previous 12 months. (3) Trait group: presumed genetic vulnerability to psychotic disorder (either schizotypal personality disorder or family history of psychotic disorder in a first degree relative). All participants were help-seeking. These UHR criteria have been published in more detail previously (Yung et al., 2003, 2004). The UHR intake criteria were assessed using the Comprehensive Assessment of At Risk Mental States (CAARMS) (Yung et al., 2005).

Exclusion criteria were: (1) medical or neurological conditions that may diminish functioning or that may account for some of the symptoms leading to the initial referral, for example, epilepsy; (2) clinically relevant biochemical or haematological abnormalities; (3) serious coexisting illnesses such as liver or renal insufficiency, significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurological or metabolic disturbances (including patients known to be HIV positive); (4) history of psychotic episodes either treated or untreated; (5) a current score of 5 or 6 on the CAARMS Mania item or a history of a previous manic episode (treated or untreated); (6) any previous use of antipsychotic (equal to or greater than a total of 5 mg of haloperidol

per week for 3 weeks or equivalent) or mood stabilizing medications; (7) history of severe drug allergy or hypersensitivity; (8) history of intellectual disability (IQ < 70); (9) and inability to understand or communicate in English.

## 2.3 | Interventions

All UHR participants received PACE TAU throughout the course of the study including psychosocial and medical treatment (Nelson et al., 2012). Psychosocial treatment at PACE consisted of supportive therapy and/or cognitive behavioural therapy (CBT) delivered within a case management framework. Medical treatment consisted of regular psychiatric reviews, medical monitoring and use of antidepressants if indicated. UHR participants in the low-dose lithium group took one slow-release 450 mg tablet of lithium carbonate each night for the entire study period in addition to PACE TAU. This dose is within the range that has been found to be consistently safe when administered to patients with bipolar disorder, depression and Alzheimer's disease (Strawbridge et al., 2023). Treatment adherence was monitored by pill count of returned medication boxes. The date that participants stopped taking trial medication was recorded. The monitoring group received PACE TAU and were followed up using the same research instruments. Monitoring of tolerability occurred at monthly intervals.

The local research and ethics committee approved the study protocol. Informed consent was obtained from all participants, and for those aged under 18 years informed consent was also obtained from a parent or guardian. Participants were made aware that they could withdraw from the study at any time and that withdrawal, or choosing not to participate in the study, would not compromise access to any standard clinical services.

## 2.4 | Measures

Side-effects were monitored using the Udvalg for Kliniske Undersogelser (UKU) side-effect checklist (Lingjaerde et al., 1987) at baseline, then every 4 weeks. The Structured Clinical Interview for DSM-IV (First & Gibbon, 2004) and the Quality of Life Scale (QLS; Heinrichs et al., 1984) were assessed at baseline only.

Secondary outcome measures were psychiatric symptoms and transition to full threshold psychotic disorder, and psychosocial functioning. Symptoms were assessed using the CAARMS (Yung et al., 2005), the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962), Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) and the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960). Transition to full threshold psychotic disorder was assessed within 12 months, with data from the PACE 400 long-term follow-up study (Nelson et al., 2013) being used to assess transition beyond this point. For participants who were lost to follow up the state public mental health records were accessed. Criteria for full threshold psychotic disorder were defined as frank positive psychotic symptoms occurring at least several times per week for 1 week or more. Transition to psychosis was assessed using the CAARMS (Yung et al., 2005). Psychosocial functioning was measured using the Global Assessment of Functioning (GAF; American Psychiatric Association, 1994).

## 2.5 | Sample size

The pilot aimed to recruit 30 UHR young people to the lithium arm, consistent with sample size recommendations for pilot studies (Cocks & Torgerson, 2013; Whitehead et al., 2016). The monitoring group was drawn from a convenience sample of young people meeting study eligibility who refused to participate in either the lithium arm or a separate medication trial (McGorry et al., 2013).

## 2.6 | Procedure

Recruitment occurred concurrently with recruitment to a trial comparing risperidone, CBT and supportive therapy (McGorry et al., 2013; Phillips et al., 2009; Yung et al., 2011). Potential participants were approached for the two intervention studies on a 1:4 basis (1 approach for the lithium trial for every 4 approaches to the risperidone, CBT, supportive therapy study). Participants received a baseline assessment prior to commencement of trial medication and could opt into the lithium arm or remain in the TAU arm. Monthly research assessments through to 12 months were undertaken consisting of the same measures administered at baseline with the addition of the UKU and with the exception of the SCID, GAF and QLS (measured at baseline only). Participants were seen weekly by the treating psychiatrist for 4 weeks and then monthly for months 2 and 3. They were seen weekly to fortnightly by their therapist/case manager for up to 12 months.

## 2.7 | Statistical methods

Side-effects attributable to lithium (as assessed by the treating doctor as being possibly, probably or very likely related to lithium treatment) were tallied at months 1, 2 and 3, and cumulatively at month 12 (i.e., the total number of participants who reported any given side-effects during the 12 month study period). Survival analysis, in particular the log-rank test, was used to compare the lithium group and the monitoring group in terms of transition rates. Analysis of covariance was used to compare the two groups in terms of the other secondary outcomes at month 3 with the corresponding baseline scores as the covariate. Psychosocial functioning was not measured at month 3 and was therefore not included in these analyses. Both last observation carried forward and multiple imputation were used as alternative ways to deal with missing values. Linear mixed effects modelling was also used to compare the two groups in terms of time trends for the secondary outcomes. Fisher's exact test was applied to carry out comparison for some categorical outcomes.

**TABLE 1** Baseline characteristic of the lithium treatment group and monitoring group.

| | | Mean | Median | SD | Min. | Max. | *n* | *p* |
|---|---|---|---|---|---|---|---|---|
| Age | Li | 20.1 | 19.0 | 3.4 | 15 | 29 | 25 | .004 |
| | Monitoring | 17.8 | 17.0 | 2.6 | 14 | 26 | 78 | |
| Duration between symptom onset and referral to PACE | Li | 286.4 | 190.0 | 287.0 | 16 | 1105 | 22 | .360 |
| | Monitoring | 358.6 | 214.5 | 417.6 | 6 | 2225 | 74 | |
| BPRS total | Li | 24.0 | 22.0 | 8.1 | 10 | 39 | 25 | .443 |
| | Monitoring | 22.4 | 21.0 | 9.6 | 2 | 57 | 77 | |
| BPRS psychotic subscale | Li | 6.5 | 7.0 | 2.0 | 3 | 10 | 25 | .155 |
| | Monitoring | 5.8 | 6.0 | 3.0 | 0 | 14 | 77 | |
| GAF score | Li | 56.6 | 60.0 | 8.2 | 35 | 68 | 25 | .881 |
| | Monitoring | 56.9 | 55.5 | 9.8 | 25 | 80 | 78 | |
| QLS total | Li | 83.4 | 87.0 | 21.0 | 33 | 109 | 25 | .179 |
| | Monitoring | 76.7 | 80.0 | 22.5 | 28 | 115 | 78 | |
| SANS affective flattening or blunting | Li | 2.6 | 2.0 | 3.1 | 0 | 11 | 25 | .089 |
| | Monitoring | 4.1 | 2.0 | 4.9 | 0 | 21 | 77 | |
| SANS alogia | Li | 1.9 | 1.0 | 2.0 | 0 | 8 | 25 | .853 |
| | Monitoring | 1.8 | 1.0 | 2.3 | 0 | 12 | 77 | |
| SANS avolition-apathy | Li | 5.0 | 5.0 | 3.7 | 0 | 12 | 25 | .307 |
| | Monitoring | 4.1 | 3.0 | 3.3 | 0 | 12 | 77 | |
| SANS anhedonia-asociality | Li | 6.4 | 5.0 | 4.1 | 0 | 14 | 25 | .783 |
| | Monitoring | 6.2 | 6.0 | 4.8 | 0 | 20 | 77 | |
| SANS attention | Li | 1.7 | 2.0 | 1.8 | 0 | 6 | 25 | .778 |
| | Monitoring | 1.8 | 1.0 | 2.1 | 0 | 8 | 77 | |
| SANS total | Li | 17.6 | 17.0 | 8.5 | 0 | 34 | 25 | .879 |
| | Monitoring | 18.0 | 14.0 | 13.1 | 0 | 55 | 77 | |
| Hamilton depression total | Li | 16.8 | 12.0 | 7.4 | 9 | 26 | 9 | .413 |
| | Monitoring | 19.2 | 19.5 | 9.4 | 2 | 36 | 50 | |

Abbreviations: BPRS, Brief Psychiatric Rating Scale; GAF, Global Assessment of Functioning; PACE, Personal Assessment and Crisis Evaluation; QLS, Quality of Life Scale; SANS, Assessment of Negative Symptoms.

## 3 | RESULTS

A total of 30 participants were recruited to the lithium arm. An additional 78 patients who met study criteria but refused participation in both this study and the other trial referred to above (McGorry et al., 2013) agreed to research assessment and follow-up (the "monitoring" group). Of the 30 participants recruited to the lithium intervention, 5 were excluded from analysis, resulting in a sample size of 25 cases. The five cases were excluded for the following reasons: identified as psychotic at baseline assessment ($n = 2$), transition to psychosis prior to any assessments being conducted ($n = 1$), below UHR threshold ($n = 1$), and no data being collected ($n = 1$).

### 3.1 | Baseline characteristics

Baseline characteristics are presented in Table 1. Both groups were found to be functionally compromised (GAF score = 56.6 in the lithium group and 56.9 in the monitoring group). The lithium group was significantly older than the monitoring group (mean age 20.1 years vs. 17.8 years, $p = .004$). The two groups did not significantly differ on any other measures.

Baseline SCID diagnoses are summarized in Table 2. There were no differences in distribution of UHR inclusion groups between the two groups, with the majority of participants meeting the APS group (see Table 2). There were significant levels of self-harm in the sample overall (72%), with no difference between the two groups (84% lithium group vs. 68% monitoring group, $p = .113$). The lithium group was found to be significantly more likely to have a forensic background compared with the monitoring group (36% vs. 6.4%, $p < .001$) as well as significantly more likely to have used illicit drugs (96% vs. 55%, $p < .001$).

### 3.2 | Lithium adherence

Across the total duration of the trial, lithium adherence ranged between 0 week (6 participants) and 44 weeks (1 participant). When

**TABLE 2** Baseline SCID diagnoses and UHR intake groups.

| | Li %(*n*) | Monitoring %(*n*) |
|---|---|---|
| Baseline SCID diagnosis | - | - |
| Major depressive disorder | 72.0 (18) | 56.4 (44) |
| Panic disorder | 16.0 (4) | 10.3 (8) |
| Generalized anxiety disorder | 8.0 (2) | 3.8 (3) |
| Social phobia | 8.0 (2) | 7.7 (6) |
| Specific phobia | 8.0 (2) | 3.8 (3) |
| Obsessive-compulsive disorder | 4.0 (1) | 6.4 (5) |
| Dysthymic disorder | 4.0 (1) | 6.4 (5) |
| Eating disorder | 0.0 (0) | 3.8 (3) |
| Other diagnoses | 8.0 (2) | 12.8 (10) |
| No diagnosis | 4.0 (1) | 23.1 (18) |
| Missing diagnosis | 4.0 (1) | 1.3 (1) |
| UHR intake groups | - | - |
| Family history only | 8.0 (2) | 16.7 (13) |
| Attenuated only | 84.0 (21) | 69.2 (54) |
| Family history and attenuated | 8.0 (2) | 9.0 (7) |
| BLIPS only | 0.0 (0) | 3.8 (3) |
| All three | 0.0 (0) | 1.3 (1) |

Abbreviations: BLIPS, brief limited intermittent psychotic symptoms; UHR, ultra-high risk.

**TABLE 3** Lithium compliance data.

| Weeks lithium adherent | % (*n*) | Cumulative % (*n*) |
|---|---|---|
| 0 | 24 (6) | 24 (6) |
| 4 | 4 (1) | 28 (7) |
| 8 | 8 (2) | 36 (9) |
| 12 | 16 (4) | 52 (13) |
| 16 | 16 (4) | 68 (17) |
| 20 | 12 (3) | 80 (20) |
| 24 | 8 (2) | 88 (22) |
| 28 | 8 (2) | 96 (24) |
| 44 | 4 (1) | 100 (25) |

examined across 12 weeks, the mean adherence time was 8.5 weeks (SD = 5.2), with 64% ($n = 16$) of participants lithium adherent for at least 12 weeks. Half of these remained adherent until week 20 (see Table 3).

## 3.3 | Lithium side-effect profile

Side-effects of any severity attributable to lithium use (assessed as 'possibly', 'probably' or 'very likely' related) were infrequent (see Table 4). Over the course of the trial, the most common side-effects were polyuria/polydipsia (24%) and diarrhoea (20%). At 12 weeks, most participants who commenced lithium use did not experience any side-effects (73.7%), while a minority experienced multiple mild and/or moderate side-effects. No participant reported severe side-effects at 12 weeks.

Given the low rate of side-effects beyond 12 weeks, side-effect data beyond this point are not reported.

## 3.4 | Secondary outcomes

### 3.4.1 | Transition to psychotic disorder

Long-term follow-up data were available for trial participants from a previously reported long-term follow-up study (Nelson et al., 2013). These follow-up data indicated that one participant in the lithium treatment group (1/25; 4%) and six in the monitoring group (6/78; 7.69%) transitioned to psychotic disorder (see Figure 1). The transition in the lithium group occurred in month 25 (2.03 years after entry). The transitions in the monitoring group occurred in month 1 ($n = 2$), month 5 ($n = 2$), month 12 ($n = 1$) and month 60 ($n = 1$) after entry. There was no significant difference in transition rates between the two groups ($p = 0.47$). As indicated in Figure 1, none of the lithium-treated participants and 5 of 78 (6.41%) participants in the monitoring group transitioned within 1 year. Fisher's exact test comparing these two rates yielded a $p$-value of 0.33.

### 3.4.2 | Symptomatic outcomes

The changes in baseline to month 3 symptoms scores are reported in Table S1. Both groups improved in symptom ratings over this time period. There were no differences between the two groups (LOCF and multiple imputation technique were used to impute the missing values for the above two time points, yielding similar results). There were no differences between groups in rates of CAARMS suicidality at month 3, Fisher's exact test $p = .140$ (Table S2).

# 4 | DISCUSSION

This is the first study to trial low-dose lithium as a preventative intervention strategy for psychosis risk and for the treatment of existing symptomology in young people at high risk of psychosis. Lithium was generally well tolerated with few prominent or severe side-effects, as reported in other studies trialling low-dose lithium (Alevizos et al., 2012; Devanand et al., 2022) and were no more frequent than those seen in trials of antipsychotic medications in UHR samples (e.g., Washida et al., 2013; Woods et al., 2007). The most prominent side-effects at month 1 were diarrhoea and decreased salivation, and while potentially disabling side-effects (e.g., tremor) were present in a minority of participants, they were at most moderate in severity. These data suggest that low-dose lithium is a potentially safe treatment approach for young people experiencing APS and may be worthy of further study in this population.

**TABLE 4** Side-effects attributable to lithium.

| | Month 1 | | | Month 2 | | | Month 3 | | | Cumulative to month 12* |
|---|---|---|---|---|---|---|---|---|---|---|
| | Commenced Li and no missing data ($n = 14$) | Commenced Li ($n = 19$) | Total sample ($n = 25$) | Commenced Li and no missing data ($n = 12$) | Commenced Li ($n = 19$) | Total sample ($n = 23$) | Commenced Li and no missing data ($n = 17$) | Commenced Li ($n = 19$) | Total sample ($n = 25$) | Total sample ($n = 25$) |
| Side-effect | % ($n$) | % ($n$) | % ($n$) | % ($n$) | % ($n$) | % ($n$) | % ($n$) | % ($n$) | % ($n$) | % ($n$) |
| Decreased salivation | 14.3 (2) | 10.5 (2) | 8.0 (2) | - | - | - | - | - | - | 16.0 (4) |
| Diarrhoea | 14.3 (2) | 15.8 (3) | 12.0 (3) | - | 5.3 (1) | 4.3 (1) | - | 10.5 (2) | 8.0 (2) | 20.0 (5) |
| Headache (including migraine) | 7.1 (1) | 5.3 (1) | 4.0 (1) | - | - | - | 5.9 (1) | 5.3 (1) | 4.0 (1) | 8.0 (2) |
| Increased salivation | - | - | - | 8.3 (1) | 5.3 (1) | 4.3 (1) | - | - | - | 8.0 (2) |
| Increased tendency to sweat | 7.1 (1) | 5.3 (1) | 4.0 (1) | - | - | - | 5.9 (1) | 5.3 (1) | 4.0 (1) | 8.0 (2) |
| Nausea/ vomiting | - | 5.3 (1) | 4.0 (1) | - | 5.3 (1) | 4.3 (1) | 5.9 (1) | 5.3 (1) | 4.0 (1) | 16.0 (4) |
| Polyuria/ polydipsia | 7.1 (1) | 5.3 (1) | 4.0 (1) | 25 (3) | 15.8 (3) | 13 (3) | 5.9 (1) | 5.3 (1) | 4.0 (1) | 24.0 (6) |
| Tremor | - | - | - | - | 10.5 (2) | 8.7 (2) | - | 10.5 (2) | 8.0 (2) | 16.0 (4) |
| Weight gain | - | - | - | 8.3 (1) | 5.3 (1) | 4.3 (1) | 5.9 (1) | 5.3 (1) | 4.0 (1) | 12.0 (3) |
| Side-effect severity | | | | | | | | | | |
| No side-effects | 57.1 (8) | 42.1 (8) | 56.0 (14) | 66.7 (8) | 47.4 (9) | 56.5 (13) | 82.4 (14) | 73.7 (14) | 80.0 (20) | NA |
| Mild | 14.3 (2) | 26.3 (5) | 20.0 (5) | 16.7 (2) | 26.3 (5) | 21.7 (5) | 5.9 (1) | 10.5 (2) | 8.0 (2) | NA |
| Moderate | 28.6 (4) | 26.3 (1) | 20.0 (5) | 16.7 (2) | 21.1 (4) | 17.4 (4) | 11.8 (2) | 15.8 (3) | 12.0 (3) | NA |
| Severe | - | 5.3 (1) | 4.0 (1) | - | 5.3 (1) | 4.3 (1) | | - | - | NA |

*Note*: Only side-effects experienced by >1 participant are reported.

Abbreviation: UKU, Udvalg for Kliniske Undersogelser.

*UKU missing data varied across data collection point responses, hence only %'s relative to $n = 25$ listed for cumulative 12-month data.

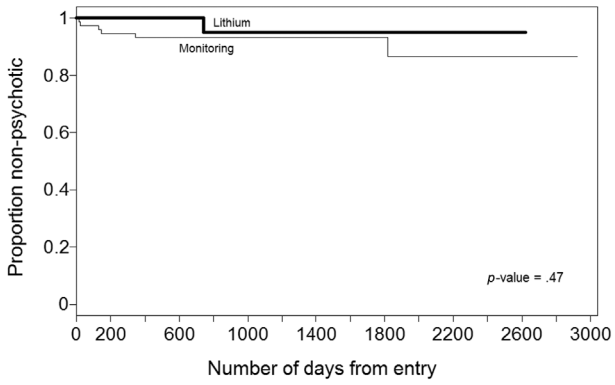


**FIGURE 1** Survival curve of transition rates in the two groups.

This high safety profile (as well as the rate of young people opting to receive lithium treatment) also has positive implications for the acceptability of low-dose lithium treatment for UHR young people, though future studies should investigate low-dose lithium's acceptability more directly. Those opting to receive lithium treatment were significantly more likely to have a forensic history (36% vs. 6.4%) and have used illicit drugs (96% vs. 55%), suggesting that those in the lithium group may have less social and occupational stability. Further investigation is warranted into why young people with these characteristics agreed to low-dose lithium treatment and whether such characteristics affected medication compliance/study dropout, since these factors are known to impact medication compliance in youth (Lambert et al., 2010).

Results failed to indicate a slower rate of transition to psychosis, or greater symptomatic and functional improvement, in those receiving low-dose lithium relative to TAU. This may in part be explained by the low rates of transition to psychosis observed across the sample (4% for lithium group, 7.7% for the monitoring group). While these transition rates approximate those reported in the NEURAPRO RCT (McGorry et al., 2017), they are lower than other UHR cohorts (Cannon et al., 2008; Morrison et al., 2012; Ruhrmann et al., 2010), including the original PACE cohort (Yung et al., 2004). For example, the 12-month transition rate was 21.8% in UHR young people receiving supportive therapy + placebo (McGorry et al., 2013).

While there were no significant group-based effects between baseline and 12 weeks, it is nonetheless positive that both the lithium and monitoring groups reported symptomatic improvement over the duration of the trial. Both groups were receiving background cognitive behavioural case management, an effective intervention for functional recovery (Lee et al., 2016) and prevention of transition to psychosis (Agbor et al., 2022), possibly introducing a ceiling effect. A network meta-analysis reported a trend-level effect for cognitive behavioural intervention, and a promising effect of family-based therapy in reducing APS (though not for antipsychotic medications or omega-3 fatty acids; Devoe et al., 2018). Given combination therapies are often recommended for complex or persistent cases, be they medication focussed such as combined antidepressant and mood stabilizer approaches (Atkin et al., 2017) or medication plus psychotherapy approaches (Lee et al., 2017), it is noteworthy that the present findings did not support differences for those receiving low-dose lithium relative to standard care. Lithium daily dosages up to 1500 mg are indicted (and tolerated) for many young people experiencing bipolar I disorder (Findling et al., 2011). While symptomatic reduction was not a primary aim of this study, it is possible that the low-dose regime used in the present study was insufficient for true symptomatic reduction.

## 4.1 | Limitations

Because the present study was a pilot, efficacy could not be investigated. Further, participant numbers were unbalanced with substantially more young people consenting to the monitoring group than low-dose lithium treatment. Medication compliance ratings were limited to assessment of returned medication not verified by lithium blood levels. Importantly, substance use was relatively crudely assessed at baseline (e.g., lifetime usage) and not assessed for the duration of the trial. It is possible that illicit substance use may interfere with the effectiveness of lithium (Jawad et al., 2018; Stokes et al., 2017), which may be especially true in the current study given the low-dose schedule. Future low-dose lithium trials should explore these questions. Those in the lithium group were significantly older than those in the monitoring group meaning potential physiological differences, especially in relation to brain maturation processes, may have impacted outcome. However, both groups were equally functionally compromised, with mean GAF scores of 57. Finally, data were collected a number of years ago. Given the lack of research on the use of low-dose lithium in UHR young people in the years since, we nevertheless consider these findings an important contribution to the literature.

## 4.2 | Conclusion

In the present open label pilot study, low-dose lithium was well-tolerated by UHR participants, with very few experiencing side-effects after 12 weeks of medication. While we found no effect of reduced time to transition or greater symptomatic and functional improvement compared with TAU, several characteristics of this study may have limited its ability to detect a treatment effect. It may also be that low-dose lithium does not reduce risk of transition to psychosis or improve symptoms over and above routine care. The present findings suggesting a larger, more rigorous trial are both feasible and safe.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## REFERENCES

Agbor, C., Kaur, G., Soomro, F. M., Eche, V. C., Urhi, A., Ayisire, O. E., Babalola, F., Eze-Njoku, C., Adaralegbe, N. J., Aladum, B., Oyeleye-Adegbite, O., & Anugwom, G. O. (2022). The role of cognitive behavioral therapy in the management of psychosis. *Cureus*, *14*(9), e28884.

Alevizos, B., Alevizos, E., Leonardou, A., & Zervas, I. (2012). Low dosage lithium augmentation in venlafaxine resistant depression: An open-label study. *Psychiatrikē = Psychiatriki*, *23*(2), 143–148.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). American Psychiatric Association.

Amminger, G. P., Berger, M., Rice, S. M., Davey, C. G., Schäfer, M. R., & McGorry, P. D. (2017). Novel biotherapies are needed in youth mental health. *Australasian Psychiatry*, *25*(2), 117–120.

Andreasen, N. C. (1983). *The scale for the assessment of negative symptoms (SANS)*. The University of Iowa.

Atkin, T., Nuñez, N., & Gobbi, G. (2017). Practitioner review: The effects of atypical antipsychotics and mood stabilisers in the treatment of depressive symptoms in paediatric bipolar disorder. *Journal of Child Psychology and Psychiatry*, *58*(8), 865–879.

Berger, G., Dell'Olio, M., Amminger, P., Cornblatt, B., Phillips, L., Yung, A., Yan, Y., Berk, M., & McGorry, P. (2007). Neuroprotection in emerging psychotic disorders. *Early Intervention in Psychiatry*, *1*(2), 114–127.

Berger, G. E., Wood, S., & McGorry, P. D. (2003). Incipient neurovulnerability and neuroprotection in early psychosis. *Psychopharmacology Bulletin*, *37*(2), 79–101.

Berger, J., Wood, S., Ross, M., Hamer, C. A., Mark Wellard, R., Pell, G., Phillips, L., Nelson, B., Amminger, G. P., Yung, R., Jackson, G., Velakoulis, D., Pantelis, C., Manji, H., & McGorry, P. D. (2012). Neuroprotective effects of low-dose lithium in individuals at ultra-high risk for psychosis. A longitudinal MRI/MRS study. *Current Pharmaceutical Design*, *18*(4), 570–575.

Cannon, T. D., Cadenhead, K., Cornblatt, B., Woods, S. W., Addington, J., Walker, E., Seidman, L. J., Perkins, D., Tsuang, M., McGlashan, T., & Heinssen, R. (2008). Prediction of psychosis in youth at high clinical risk: A multisite longitudinal study in North America. *Archives of General Psychiatry*, *65*(1), 28–37.

Cocks, K., & Torgerson, D. J. (2013). Sample size calculations for pilot randomized trials: a confidence interval approach. *Journal of Clinical Epidemiology*, *66*(2), 197–201.

Cornblatt, B. A., Lencz, T., & Kane, J. M. (2001). Treatment of the schizophrenia prodrome: Is it presently ethical? *Schizophrenia Research*, *51*(1), 31–38.

Davies, C., Cipriani, A., Ioannidis, J. P., Radua, J., Stahl, D., Provenzani, U., McGuire, P., & Fusar-Poli, P. (2018). Lack of evidence to favor specific preventive interventions in psychosis: A network meta-analysis. *World Psychiatry*, *17*(2), 196–209.

Davies, C., Radua, J., Cipriani, A., Stahl, D., Provenzani, U., McGuire, P., & Fusar-Poli, P. (2018). Efficacy and acceptability of interventions for attenuated positive psychotic symptoms in individuals at clinical high risk of psychosis: A network meta-analysis. *Frontiers in Psychiatry*, *9*, 187.

Devanand, D. P., Crocco, E., Forester, B. P., Husain, M. M., Lee, S., Vahia, I. V., Andrews, H., Simon-Pearson, L., Imran, N., Luca, L., Huey, E. D., Deliyannides, D. A., & Pelton, G. H. (2022). Low dose lithium treatment of behavioral complications in Alzheimer's disease: Lit-AD randomized clinical trial. *The American Journal of Geriatric Psychiatry*, *30*(1), 32–42. https://doi.org/10.1016/j.jagp.2021.04.014

Devoe, D. J., Farris, M. S., Townes, P., & Addington, J. (2018). Attenuated psychotic symptom interventions in youth at risk of psychosis: A systematic review and meta-analysis. *Early Intervention in Psychiatry*, *13*, 3–17.

Findling, R. L., Kafantaris, V., Pavuluri, M., McNamara, N. K., McClellan, J., Frazier, J. A., Sikich, L., Kowatch, R., Lingler, J., Faber, J., Rowles, B. M., Clemons, T. E., & Taylor-Zapata, P. (2011). Dosing strategies for lithium monotherapy in children and adolescents with bipolar I disorder. *Journal of Child and Adolescent Psychopharmacology*, *21*(3), 195–205.

First, M. B., & Gibbon, M. (2004). The structured clinical interview for DSM-IV axis I disorders (SCID-I) and the structured clinical interview for DSM-IV axis II disorders (SCID-II). In M. J. Hilsenroth & D. L. Segal (Eds.), *Comprehensive handbook of psychological assessment* (Vol. 2, pp. 134–143). John Wiley & Sons, Inc.

Gifford, G., Crossley, N., Fusar-Poli, P., Schnack, H. G., Kahn, R. S., Koutsouleris, N., Cannon, T. D., & McGuire, P. (2017). Using neuroimaging to help predict the onset of psychosis. *NeuroImage*, *145*, 209–217.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*, *23*, 56–62.

Hartmann, J. A., Nelson, B., Ratheesh, A., Treen, D., & McGorry, P. D. (2018). At-risk studies and clinical antecedents of psychosis, bipolar disorder and depression: A scoping review in the context of clinical staging. *Psychological Medicine*, *49*(2), 1–13.

McGorry, P. D., Hartmann, J. A., Spooner, R., & Nelson, B. (2018). Beyond the "at risk mental state" concept: Transitioning to transdiagnostic psychiatry. *World Psychiatry*, *17*(2), 133–142.

Heinrichs, D., Hanlon, T., & Carpenter, W. (1984). The Quality of Life Scale: An instrument for rating the schizophrenia deficit syndrome. *Schizophrenia Bulletin*, *10*, 388–398.

Jarskog, L. F., Glantz, L. A., Gilmore, J. H., & Lieberman, J. A. (2005). Apoptotic mechanisms in the pathophysiology of schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *29*(5), 846–858.

Jawad, I., Watson, S., Haddad, P. M., Talbot, P. S., & McAllister-Williams, R. H. (2018). Medication nonadherence in bipolar disorder: A narrative review. *Therapeutic Advances in Psychopharmacology*, *8*, 349–363.

Kempton, M. J., & McGuire, P. (2015). How can neuroimaging facilitate the diagnosis and stratification of patients with psychosis? *European Neuropsychopharmacology*, *25*(5), 725–732.

Keshavan, M. S., Anderson, S., & Pettegrew, J. W. (1994). Is schizophrenia due to excessive synaptic pruning in the prefrontal cortex? The Feinberg hypothesis revisited. *Journal of Psychiatric Research*, *28*(3), 239–265.

Keshavan, M. S., Berger, G., Zipursky, R. B., Pantelis, C., & Wood, S. J. (2005). Neurobiology of early psychosis. *The British Journal of Psychiatry*, *187*(S48), s8–s18.

Lambert, M., Conus, P., Cotton, S., Robinson, J., McGorry, P. D., & Schimmelmann, B. G. (2010). Prevalence, predictors, and consequences of long-term refusal of antipsychotic treatment in first-episode psychosis. *Journal of Clinical Psychopharmacology*, *30*(5), 565–572.

Lee, G.-Y., Yu, H.-Y., Jhon, M., & Yoon, J.-S. (2016). Intensive cognitive behavioral case management for functional recovery of young patients with schizophrenia. *Korean Journal of Schizophrenia Research*, *19*(1), 32–37.

Lee, J., Hearon, B. A., & Otto, M. W. (2017). Combined treatment with CBT and psychopharmacology. In *The science of cognitive behavioral therapy* (pp. 131–153). Elsevier.

Lingjaerde, O., Ahlfors, U. G., Bech, P., Dencker, S. J., & Elgen, K. (1987). The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatrica Scandinavica*, *76*, 85–94.

Malhi, G. S., & Outhred, T. (2016). Therapeutic mechanisms of lithium in bipolar disorder: Recent advances and current understanding. *CNS Drugs*, *30*(10), 931–949.

Manji, H. K., Moore, G. J., & Chen, G. (1999). Lithium at 50: Have the neuroprotective effects of this unique cation been overlooked? *Biological Psychiatry*, *46*(7), 929–940.

Manji, H. K., Moore, G. J., & Chen, G. (2000). Clinical and preclinical evidence for the neurotrophic effects of mood stabilizers: Implications for the pathophysiology and treatment of manic-depressive illness. *Biological Psychiatry*, *48*(8), 740–754.

Manji, H. K., Moore, G. J., Rajkowska, G., & Chen, G. (2000). Neuroplasticity and cellular resilience in mood disorders. *Molecular Psychiatry*, *5*(6), 578–593.

McGorry, P. D., Nelson, B., Phillips, L. J., Yuen, H. P., Francey, S. M., Thampi, A., Berger, G. E., Amminger, G. P., Simmons, M. B., Kelly, D., Dip, G., Thompson, A. D., & Yung, A. R. (2013). Randomized controlled trial of interventions for young people at ultra-high risk of psychosis: Twelve-month outcome. *The Journal of Clinical Psychiatry.*, *74*, 349–356.

McGorry, P. D., Nelson, B., Markulev, C., Yuen, H. P., Schäfer, M. R., Mossaheb, N., Schlögelhofer, M., Smesny, S., Hickie, I. B., Berger, G. E., Chen, E. Y. H., de Haan, L., Nieman, D. H., Nordentoft, M., Riecher-Rössler, A., Verma, S., Thompson, A., Yung, A. R., & Amminger, G. P. (2017). Effect of ω-3 polyunsaturated fatty acids in young people at ultrahigh risk for psychotic disorders: The NEURAPRO randomized clinical trial. *JAMA Psychiatry*, *74*(1), 19–27.

McGorry, P., Keshavan, M., Goldstone, S., Amminger, P., Allott, K., Berk, M., Lavoie, S., Pantelis, C., Yung, A., Wood, S., & Hickie, I. (2014). Biomarkers and clinical staging in psychiatry. *World Psychiatry*, *13*(3), 211–223.

Mei, C., van der Gaag, M., Nelson, B., Smit, F., Yuen, H. P., Berger, M., Krcmar, M., French, P., Amminger, G. P., Bechdolf, A., Cuijpers, P., Yung, A. R., & McGorry, P. D. (2021). Preventive interventions for individuals at ultra high risk for psychosis: An updated and extended meta-analysis. *Clinical Psychology Review*, *86*, 102005.

Moore, G. J., Bebchuk, J. M., Hasanat, K., Chen, G., Seraji-Bozorgzad, N., Wilds, I. B., Faulk, M. W., Koch, S., Glitz, D. A., Jolkovsky, L., & Manji, H. K. (2000). Lithium increases N-acetyl-aspartate in the human brain: In vivo evidence in support of bcl-2's neurotrophic effects? *Biological Psychiatry*, *48*(1), 1–8.

Moore, G. J., Bebchuk, J. M., Wilds, I. B., Chen, G., & Manji, H. K. (2000). Lithium-induced increase in human brain grey matter. *Lancet*, *356*(9237), 1241–1242.

Morén, C., Treder, N., Martínez-Pinteño, A., Rodríguez, N., Arbelo, N., Madero, S., Mas, S., Gassó, P., & Parellada, E. (2022). Systematic review of the therapeutic role of apoptotic inhibitors in neurodegeneration and their potential use in schizophrenia. *Antioxidants*, *11*(11), 2275–2298.

Morrison, A. P., French, P., Stewart, S. L., Birchwood, M., Fowler, D., Gumley, A. I., Jones, P. B., Bentall, R. P., Lewis, S. W., Murray, G. K., Patterson, P., Brunet, K., Conroy, J., Parker, S., Reilly, T., Byrne, R., Davies, L. M., & Dunn, G. (2012). Early detection and intervention evaluation for people at risk of psychosis: Multisite randomised controlled trial. *BMJ*, *344*, e2233.

Nelson, B., Yuen, H. P., Wood, S. J., Lin, A., Spiliotacopoulos, D., Bruxner, A., Broussard, C., Simmons, M., Foley, D. L., Brewer, W. J., Francey, S. M., Amminger, G. P., Thompson, A., McGorry, P. D., & Yung, A. R. (2013). Long-term follow-up of a group at ultra high risk ("prodromal") for psychosis: The PACE 400 study. *JAMA Psychiatry*, *70*(8), 793–802.

Nelson, B., Thompson, A., Jung, A., & McGorry, P. (2012). *The PACE clinic manual: A treatment approach for young people at ultra high risk of psychosis*. Orygen Youth Health Research Centre.

Overall, J., & Gorham, D. (1962). The brief psychiatric rating scale. *Psychological Reports*, *10*, 799–812.

Pantelis, C., Velakoulis, D., McGorry, P. D., Wood, S. J., Suckling, J., Phillips, L. J., Yung, A. R., Bullmore, E. T., Brewer, W., Soulsby, B., Desmond, P., & McGuire, P. K. (2003). Neuroanatomical abnormalities before and after onset of psychosis: A cross-sectional and longitudinal MRI comparison. *Lancet*, *361*(9354), 281–288.

Pantelis, C., Yucel, M., Wood, S. J., Velakoulis, D., Sun, D., Berger, G., Stuart, G. W., Yung, A., Phillips, L., & McGorry, P. D. (2005). Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. *Schizophrenia Bulletin*, *31*(3), 672–696.

Phillips, L. J., Nelson, B., Yuen, H. P., Francey, S. M., Simmons, M., Stanford, C., Ross, M., Kelly, D., Baker, K., Conus, P., Amminger, P., Trumpler, F., Yun, Y., Lim, M., McNab, C., Yung, A. R., & McGorry, P. D. (2009). Randomized controlled trial of interventions for young people at ultra-high risk of psychosis: Study design and baseline characteristics. *Australian and New Zealand Journal of Psychiatry*, *43*(9), 818–829.

Ruhrmann, S., Schultze-Lutter, F., Salokangas, R. K., Heinimaa, M., Linszen, D., Dingemans, P., Birchwood, M., Patterson, P., Juckel, G., Heinz, A., Morrison, A., Lewis, S., von Reventlow, H. G., & Klosterkötter, J. (2010). Prediction of psychosis in adolescents and young adults at high risk: Results from the prospective. *European Prediction of Psychosis Study*, *67*(3), 241–251.

Stafford, M. R., Jackson, H., Mayo-Wilson, E., Morrison, A. P., & Kendall, T. (2013). Early interventions to prevent psychosis: Systematic review and meta-analysis. *BMJ*, *346*, f185.

Stokes, P. R., Kalk, N. J., & Young, A. H. (2017). Bipolar disorder and addictions: The elephant in the room. *The British Journal of Psychiatry*, *211*(3), 132–134.

Strawbridge, R., Kerr-Gaffney, J., Bessa, G., Loschi, G., Freitas, H. L. O., Pires, H., Cousins, D. A., Juruena, M. F., & Young, A. H. (2023). Identifying the neuropsychiatric health effects of low-dose lithium interventions: A systematic review. *Neuroscience & Biobehavioral Reviews*, *144*, 104975.

van der Gaag, M., Smit, F., Bechdolf, A., French, P., Linszen, D. H., Yung, A. R., McGorry, P., & Cuijpers, P. J. S. R. (2013). Preventing a first episode of psychosis: Meta-analysis of randomized controlled prevention trials of 12month and longer-term follow-ups. *Schizophrenia Research*, *149*(1–3), 56–62.

Warner, R. (2001). The prevention of schizophrenia: What interventions are safe and effective? *Schizophrenia Bulletin*, *27*(4), 551–562.

Washida, K., Takeda, T., Habara, T., Sato, S., Oka, T., Tanaka, M., Yoshimura, Y., & Aoki, S. (2013). Efficacy of second-generation antipsychotics in patients at ultra-high risk and those with first-episode or multi-episode schizophrenia. *Neuropsychiatric Disease and Treatment*, *9*, 861–868.

Whitehead, A. L., Julious, S. A., Cooper, C. L., & Campbell, M. J. (2016). Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. *Statistical Methods in Medical Research*, *25*(3), 1057–1073.

Woods, S. W., Tully, E. M., Walsh, B. C., Hawkins, K. A., Callahan, J. L., Cohen, S. J., Mathalon, D. H., Miller, T. J., & McGlashan, T. H. (2007). Aripiprazole in the treatment of the psychosis prodrome: An open-label pilot study. *The British Journal of Psychiatry. Supplement*, *51*, s96–s101.

Yung, A. (2007). Identification and treatment of the prodromal phase of psychotic disorders: Perspectives from the PACE clinic. *Early Intervention in Psychiatry*, *1*(3), 224–235.

Yung, A., McGorry, P. D., Francey, S. M., Nelson, B., Baker, K., Phillips, L. J., Berger, G., & Amminger, G. P. (2007). PACE: A specialised service for young people at risk of psychotic disorders. *Medical Journal of Australia*, *187*(7), S43.

Yung, A., Pan Yuen, H., Mcgorry, P. D., Phillips, L. J., Kelly, D., Dell'Olio, M., Francey, S. M., Cosgrave, E. M., Killackey, E., Stanford, C., Godfrey, K., & Buckby, J. (2005). Mapping the onset of psychosis: The comprehensive assessment of At-risk mental states. *Australian and New Zealand Journal of Psychiatry*, *39*(11–12), 964–971.

Yung, A., Phillips, L. J., Nelson, B., Francey, S. M., Yuen, H. P., Simmons, M. B., Ross, M. L., Kelly, D., Baker, K., Paul Amminger, G., Berger, G., Thompson, A. D., Thampi, A., & McGorry, P. D. (2011). Randomized controlled trial of interventions for young people at ultra high risk for psychosis: 6-month analysis. *Journal of Clinical Psychiatry*, *72*(4), 430–440.

Yung, A., Phillips, L. J., Yuen, H. P., Francey, S. M., McFarlane, C. A., Hallgren, M., & McGorry, P. D. (2003). Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. *Schizophrenia Research*, *60*(1), 21–32.

Yung, A., Phillips, L. J., Yuen, H. P., & McGorry, P. D. (2004). Risk factors for psychosis in an ultra high-risk group: Psychopathology and clinical features. *Schizophrenia Research*, *67*(2–3), 131–142.

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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