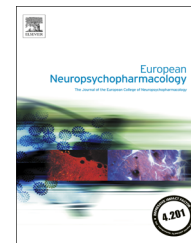




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# Glycine treatment of the risk syndrome for psychosis: Report of two pilot studies <sup>☆</sup>



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## Abstract

Patients meeting criteria for the risk syndrome for psychosis have treatment needs including positive and negative symptoms and cognitive impairment. These features could potentially respond to NMDA glycine-site agonists. The present objective was to determine which symptoms or domains of cognition promise to show the greatest response to glycine in risk syndrome patients. We conducted two short-term pilot studies of glycine used without adjunctive antipsychotic medication. In the first trial, 10 risk syndrome subjects received open-label glycine at doses titrated to 0.8 g/kg/d for 8 weeks, followed by discontinuation and 16 weeks of evaluation for durability of effects. In the second, 8 subjects were randomized to double-blind glycine vs. placebo for 12 weeks, followed by open-label glycine for another 12 weeks. Patients were evaluated every 1-2 weeks with the Scale Of Psychosis-risk Symptoms (SOPS) and before and after treatment with a neurocognitive battery. Within-group and between-group effect sizes were calculated. Effect sizes were large for positive (open-label within-group  $-1.10$ , double-blind between-group  $-1.11$ ) and total ( $-1.39$  and  $-1.15$ ) symptoms and medium-to-large ( $-0.74$  and  $-0.79$ ) for negative symptoms. Medium or large effect sizes were also observed for several neurocognitive measures in the open-label study, although data were sparse. No safety concerns were identified. We conclude that glycine was associated with reduced symptoms with promising effect sizes in two pilot studies and a

<sup>☆</sup>Trial Registration: These studies have the ClinicalTrials.gov identifiers: NCT00268749 and NCT00291226.

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possibility of improvement in cognitive function. Further studies of agents that facilitate NMDA receptor function in risk syndrome patients are supported by these preliminary findings.  
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## 1. Introduction

The *N*-methyl-*D*-aspartate receptor (NMDAR) hypoactivity model is a leading hypothesis about the neurobiology of schizophrenia (Javitt and Zukin, 1991; Kantrowitz and Javitt, 2010; Kim et al., 1980; Krystal et al., 2002; Olney et al., 1999). This hypothesis is based in part on exacerbation of positive and negative symptoms and cognitive impairment in schizophrenia patients by NMDAR antagonists such as ketamine and the production of similar effects in healthy humans. Evidence suggests NMDAR hypoactivity may connect to other prominent models of psychosis (Feinberg, 1982; Howes and Kapur, 2009; McGlashan and Hoffman, 2000) by contributing to the development of dopamine hyperactivity in striatum (Carlsson et al., 1999; Laruelle et al., 2003) and cortical synaptic plasticity deficits (Collingridge and Singer, 1990; Newcomer and Krystal, 2001; Olney et al., 1999; Shi et al., 1999).

Over the past 15 years, researchers have attempted to identify patients in the prodromal phase of psychotic disorders prospectively, based primarily on subsyndromal psychotic-like or “attenuated” positive symptoms (Miller et al., 2002; Yung et al., 1996). Since the term “prodrome” traditionally carries a retrospective connotation, the alternative terms “risk syndrome for psychosis” (Woods et al., 2009), “at-risk mental state,” “ultra high risk,” “clinical high risk,” and most recently “attenuated psychosis syndrome” or “APS” (Carpenter and van Os, 2011) have been proposed. A recent meta-analysis of 27 studies suggested that the average rate of transition to full psychosis among such patients is 22% by one year and 36% by three years (Fusar-Poli et al., 2012). Structural thinning of cerebral cortex (Pantelis et al., 2003) and increased striatal uptake of dopamine precursor (Howes et al., 2011), neurobiological findings typical of established schizophrenia, have been reported at baseline in risk syndrome patients who later progress to psychosis, findings which increase in magnitude after progression to psychosis has occurred.

In addition to carrying substantial risk for transition to frank psychosis, risk syndrome patients meet general mental health standards for current illness (Ruhmann et al., 2010) in that at presentation they display distressing current symptoms and functional and cognitive impairment (Woods et al., 2001, 2010). Intervention studies have begun to address these patients’ prevention needs (Amminger et al., 2010; McGlashan et al., 2006; McGorry et al., 2002; Morrison et al., 2004; Yung et al., 2011), and some have started to investigate current clinical state as a treatment target (Amminger et al., 2010; McGorry et al., 2002; Ruhmann et al., 2007; Woods et al., 2003, 2007; Yung et al., 2011). Medication treatment studies have primarily focused on use of antipsychotics, but there is a compelling need for investigation of other treatments with fewer adverse effects such as the current effort and the recent omega-3 fatty acid study (Amminger et al., 2010).

Glycine is an amino acid neurotransmitter in brain that acts at the glycine/*D*-serine modulatory site on the NMDAR

as a full coagonist with glutamate (Javitt, 2006). Based on the hypothesis that the risk syndrome may reflect an NMDAR hypofunction state, we tested the therapeutic effects of glycine in risk syndrome patients in two small, short-term pilot studies initiated in preparation for future more definitive trials.

## 2. Experimental procedures

The first pilot study assessed whether the size of any beneficial effect of glycine in this population promises to be clinically meaningful (Kraemer et al., 2006) and what might best be identified as the principal therapeutic target in future studies. An open-label design was employed. Since within-active-drug effect sizes in psychosis can be lower with placebo-controlled designs than when only active medication is employed (Woods et al., 2005), we also conducted a second small placebo-controlled study with similar aims. Glycine was used in both studies without adjunctive antipsychotic medication.

### 2.1. Subjects

Potential subjects or their families or providers were informed about the symptoms of the risk syndrome for psychosis through a variety of ongoing community education efforts and were invited to call our research clinic if concerned. Adult subjects gave written informed consent, and minors gave written informed assent with consent from a parent or guardian. Subjects were included in either study if they were treatment-seeking outpatients 14 to 35 years old who met diagnostic criteria for a possible risk syndrome (see below). Subjects were excluded for any of the following reasons: (1) past or current DSM IV criteria for any lifetime psychotic disorder, (2) judged clinically to suffer from a psychiatric disorder (e.g., mania, depression, ADHD) which could account for the inclusion symptoms, (3) presented with inclusion symptoms occurring primarily as sequelae to drug or alcohol use, (4) alcohol or drug abuse or dependence in the past three months, (5) use of antipsychotic medication in the previous three months, (6) change in dosage of any antidepressant, anxiolytic, psychostimulant, or mood stabilizer medication within eight weeks.

The Criteria of Psychosis-risk Syndromes (COPS) diagnostic criteria were used to identify subjects as eligible (McGlashan et al., 2010). The COPS criteria are based primarily on subthreshold levels of positive symptoms and operationally define three risk syndromes originally articulated by the Melbourne group (Yung et al., 1996): Attenuated Positive Symptom Syndrome, Brief Intermittent Psychotic Syndrome, and Genetic Risk and Recent Functional Decline Syndrome. The rationale for these syndromes, their definitions, and evidence for their reliability and validity have been published previously in detail (Addington et al., 2007; Miller et al., 2002, 2003; Woods et al., 2009). The Attenuated Positive Symptom Syndrome usually accounts for the preponderance of the cases. In general, positive symptoms are considered subsyndromal or “attenuated” when they remain relatively unformed, relatively infrequent, and are identified by the subject as possibly a trick of their imagination (McGlashan et al., 2010). Both studies required a minimum total score of 20 on the Scale of Psychosis-risk Symptoms (SOPS, see Assessments) for inclusion.

### 2.2. Study design

Subjects were enrolled in the first study between February 2003 and May 2004 and in the second study between March 2006 and May

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