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The early identification of psychosis: Can lessons be learnt from Cardiac Stress Testing?

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Abstract

Psychotic disorders including schizophrenia are amongst the most debilitating psychiatric disorders. There is an urgent need to develop methods to identify individuals at risk with greater precision and as early as possible. At present, a prerequisite for a diagnosis of schizophrenia is the occurrence of a psychotic episode. Therefore, attempting to detect schizophrenia on the basis of psychosis is analogous to diagnosing coronary artery disease (CAD) *after* the occurrence of a myocardial infarction (MI). The introduction of cardiac stress testing (CST) has revolutionized the detection of CAD and the prevention and management of angina and MI.

In this paper we attempt to apply lessons learnt from cardiac stress testing to the early detection of psychosis by proposing the development of an analogous psychosis stress test.

We discuss in detail the various parameters of a proposed psychosis stress test including the choice of a suitable psychological or psychopharmacological “stressor”, target population, outcome measures, safety of the approach and the necessary evolution of test to become clinically informative.

The history of evolution of CST may guide the development of a similar approach for the detection and management of psychotic disorders. The initial development of a test to unmask latent risk for schizophrenia will require the selection of a suitable and safe stimulus and the development of outcome measures as a prelude to testing in populations with a range of risk to determine predictive value. The use of cardiac stress testing in coronary artery disease offers the intriguing possibility that a similar approach may be applied to the detection and management of schizophrenia.

Keywords

coronary artery disease; schizophrenia; psychosis; risk; diagnosis

“If risk (for schizophrenia) is analogous to hyperlipidemia, prodrome comparable to angina, then psychosis can be thought of as myocardial infarction with frequent residual loss of function” (from Rethinking Schizophrenia: Insel (2010))

Introduction

Psychotic disorders like schizophrenia, remain the most debilitating of psychiatric disorders. There is an urgent need to develop better methods to identify individuals at risk for schizophrenia, and to identify them as early as possible to create opportunities for intervention. To fulfill this purpose, these methods should possess high positive predictive value (PPV) and should be able to identify at risk individuals early enough before the clinical presentation of their disease.

The committee on prevention of mental disorders classified prevention initiatives as universal, selective and indicated (Mrazek and Haggerty 1994). As originally defined by (Gordon 1983), whereas universal preventive measures are desirable for the entire eligible population, selective preventive measures are desirable only to those whose risk of becoming ill is above average. Indicated preventive measure applies to persons who, on examination, are found to manifest a risk factor, condition, or abnormality that identifies them, individually, as being at high risk for the future development of a disease. For diseases with complex, multifactorial etiologies, like coronary artery disease (CAD) universal, selective and indicated approaches have proved highly successful. The indicated preventive measures in CAD have been successful primarily due to the availability of sensitive screening tests that could *identify* vulnerable individuals before their disease became obvious and *stratify* their risk for disease. In keeping with these approaches to prevention, there are growing efforts to identify individuals at risk for psychotic disorders and to intervene with the goal of preventing, delaying or attenuating the illness (van der Gaag et al. 2013). In psychotic disorders such as schizophrenia universal, selective and indicated preventive measures would be applied as outlined in table 1. Selective preventive measures would be applied to those who have a higher risk of developing psychosis, such as family members of individuals with psychosis. Indicated preventive measures would be applied in individuals who have not developed a diagnosable psychotic illness but clearly manifest a clinical abnormality indicative of an underlying pathological process such as basic symptoms or a decline in functioning.

Although several risk factors including a positive family history (Kendler et al. 1985), a complicated obstetric history (Cannon et al. 2002), cannabis exposure (Radhakrishnan et al. 2014), vitamin D deficiency at birth (McGrath et al. 2010), social skill deficits and IQ deficits (Davidson et al. 1999) in childhood have been none of these individually or in combination have been shown to predict psychosis before the individual actually develops transient or attenuated psychotic symptoms or a significant reduction in functioning. If we liken these risk factors to hyperlipidemia (a risk factor for CAD) then the basic symptoms psychotic are analogous to chest pain (Fusar-Poli et al. 2013). Ideally, we would be able to apply selective preventive measures in individuals who possess these risk factors for schizophrenia before they have developed any psychotic symptoms (or “chest pain”). However, current strategies in the early detection of schizophrenia are limited to the

prediction of transition to psychosis in individuals who already have transient or attenuated psychotic symptoms, or a significant reduction in functioning. We propose the development of a psychosis stress test that could identify individuals in a stage where selective interventions would be effective in preventing the development of psychotic symptoms or that could be instituted before the manifestation of symptoms. Such an approach would need to rely on the use of biomarkers since relying on symptoms might be too late.

Several biomarkers of risk for schizophrenia have been identified although none of them are sufficiently sensitive or specific, and therefore, further research is necessary to establish their predictive value (Johnstone et al. 2005; Lawrie et al. 2001; McGorry 2014; Sorensen et al. 2006). Neurocognitive testing (Pukrop et al. 2007), structural brain imaging (Wood et al. 2008) and both conventional (Gschwandtner et al. 2009) and quantitative (van Tricht et al. 2014) analyses of EEG have been used independently to differentiate individuals at risk for psychosis who will transition to psychosis from those who will not (table 2). While it is out of the scope of this paper to review all the approaches, we provide some examples of these approaches. Meta-analyses of clinically high risk (CHR) for psychosis individuals revealed that they had small to medium impairments in a wide range of neurocognitive domains (Giuliano et al. 2012; Woodberry et al. 2008) and that transition to psychosis is particularly associated with deficits in verbal fluency and memory functioning (Fusar-Poli et al. 2012). Single subject structural imaging using support vector machines has been gaining ground in separating schizophrenia from affective disorders and for the identification of individuals at high risk for psychosis (Koutsouleris et al. 2015). Multivariate analysis of neuroanatomical patterns using support vector machines has been applied to classify subjects at-risk mental state (ARMS) for psychosis who transitioned to psychosis (Koutsouleris et al. 2009). Quantitative EEG analyses in the European Prediction of Psychosis Study categorized CHR subjects into three risk classes with the class III having a significantly higher hazard rate compared to risk class I and II (van Tricht et al. 2014). More recently, attempts to improve predictive accuracy have used combinations of behavioral, cognitive, electrophysiological, structural and functional neuroimaging data (table 2). For example, combining negative symptoms with EEG power in the theta band correctly classified 89% of ARMS who transitioned to psychosis (Zimmermann et al. 2010).

These advances in refining the prediction of transition to psychosis in individuals who have already been identified as high risk based on the presence of sub-threshold psychotic symptoms are important. However, there remains a critical need to identify those at high risk even earlier than the prevailing approaches allow, i.e., *before* the emergence of psychotic symptoms. The development of more sensitive and specific approaches applied to both the earliest detection of risk for schizophrenia in the general population and the prediction of conversion in high-risk individuals might alter the risk-benefit ratio in favor of psychosocial and pharmacological interventions directed towards individuals with the highest risk for schizophrenia.

Could the development of cardiac stress testing (CST) as a tool for early detection of CAD inform the development of a similar strategy for schizophrenia?

CST has revolutionized the early detection and management of CAD and prevention of MI. Schizophrenia is a complex disorder that shares some similarities with CAD including the existence of modifiable (e.g. drug use) and non-modifiable (e.g. genetics) risk factors. Existing screening programs identify vulnerable populations primarily based on family history of schizophrenia or attenuated psychotic symptoms, which is analogous to relying on family history of CAD or symptoms (chest pain) to identify those at risk for CAD. Currently, a prerequisite for a diagnosis of schizophrenia is the occurrence of a psychotic (American Psychiatric Association 2000). This is similar to diagnosing CAD *after* the occurrence of a MI and is too late for most preventive measures. As stated by Thomas Insel (Insel 2010) in 'Rethinking Schizophrenia' "If risk (for schizophrenia) is analogous to hyperlipidemia, prodrome comparable to angina, then psychosis can be thought of as myocardial infarction with frequent residual loss of function".

Below, herewith we briefly review the evolution of CST from its inception into its current form with a view towards informing the development of a similar approach for schizophrenia.

Cardiac Stress Testing

refers to tests focused on stressing an individual's cardiovascular system either through physical exercise, pharmacological stimulation or both so as to unmask compromised coronary circulation. Coronary hypoperfusion manifests as chest pain or discomfort, and alterations in heart rate, blood pressure and EKG - parameters that are monitored throughout the test. As CST has evolved over the years, physical exercise protocols have been standardized and newer and more sensitive markers of coronary hypoperfusion are being used. This has made CST more sensitive and specific for CAD and has improved the safety of testing (Gibbons et al. 2002).

The evolution of cardiac stress testing from a research to a clinical tool

The clinical utility of CST has been greatly enhanced by the refinement of the stimulus parameters, outcome measures and risk stratification of the patients who undergo CST. Before the 1930s, CST was used primarily as a research tool and its clinical use in diagnosing latent myocardial ischemia was first proposed around 1950 by Wood (Wood et al. 1950) and Hecht (1949). Bruce proposed the stratification of patients into New York Heart Disease Classification groups I-IV based on criteria established by treadmill CST (Bruce et al. 1963). This was followed by the demonstration that the predictive value of ST-segment depression for future coronary events was even higher than the predictive value of clinical history (Robb and Marks 1967). In the ensuing years, several groups (Balcon et al. 1968; Lewis and Wilson 1971; Martin and McConahay 1972; Najmi et al. 1968) demonstrated a correlation between coronary angiographic data, which is the gold standard for confirming CAD diagnosis, and ST-segment changes during CST. Formal guidelines

have specified indications and contra-indications for the test, interpretations of the results, risk stratification and indications for termination (Fletcher 1997; Gibbons et al. 1997).

Development and Refinement of Stimuli for cardiac stress testing

The initial stimulus for CST was relatively crude – patients were required to perform sit-ups while their symptoms and vital signs were monitored (Feil H 1928). This was followed by individualization of the exercise-load to meet each patient's capacity (Wood et al. 1950), the development of the nine-inch step (Missal 1938), the use of the treadmill or bicycle (Northridge et al. 1990) and standardized exercise protocols like the Bruce protocol (Bruce et al. 1963; Taylor et al. 1955; Taylor et al. 1963). Pharmacological agents e.g., dipyridamole (Iskandrian et al. 1988), dobutamine (Mason et al. 1984) and adenosine (Nguyen et al. 1990) to stress the cardiovascular system are being increasingly used, especially when performance of a conventional exercise test is impractical.

Development and Refinement of Outcomes for cardiac stress testing (CST)

Self-reported outcomes

In the early years, the outcome measures used in CST were almost exclusively comprised of self-reports of subjective effects: chest pain or discomfort. Given the high predictive value of chest pain, the emergence of chest pain during CST was also an endpoint.

Objective Outcomes

The recognition that exercise-induced hypoperfusion in CAD patients was associated with ST-segment depression on the EKG and with chest pain was pivotal in adopting an objective outcome – a biomarker. Riseman introduced the concept of continuous EKG monitoring that led to the recognition that ST-segment depression preceded the onset of pain and persisted beyond the duration of pain (Riseman JEF 1940). Since then, imaging techniques like thallium scintigraphy which measure cardiac perfusion and echocardiography which measures ventricular function have been developed and incorporated into CST and are now used in the calculation of the risk for CAD. Accordingly, the American Heart Association guidelines (Gibbons et al. 1997) stated that that interpretation of the CST should include objective outcomes of exercise capacity (distance traversed, incline), changes in vital signs (e.g. blood pressure, heart rate), EKG (e.g. ST segment depression), coronary perfusion (scintigraphy), cardiac function (echocardiogram) etc. The nuclear stress test is generally considered to be the most accurate type of stress test with a specificity of ~81% and sensitivity of ~90%.

Over time, with the wide implementation of CST, the use and quantification of specific outcome measures and their value in predicting CAD have become well-defined.

The Target Population for CST

The population at risk for CAD is stratified based on several clinical parameters including demographic information, symptoms (e.g., chest pain), family history of CAD and related risks and current medical history and laboratory tests (Diamond and Forrester 1979) into low, intermediate and high-risk categories. CST has the greatest utility in diagnosis and

prognosis of CAD in individuals identified as having intermediate risk for CAD i.e. in individuals who have angina but have not had an MI yet (prodromal symptoms but no psychotic episode). However, the AHA guidelines (Fletcher et al. 2013) recommend the use of CST also in individuals who have risk factors for CAD but have not had developed angina yet (risk factors but no prodromal symptoms). This process of identification of the population that would benefit greatest from CST has taken time and importantly, has involved updating the risk stratification as newer risk factors have been recognized.

CST has high negative and positive predictive value for cardiac events after the occurrence of MI. For example, following an MI, the negative predictive value (NPV) for another MI and cardiac death was 98.8% over 36 months of follow-up for myocardial perfusion imaging and 98.4% over 33 months for echocardiography (Metz et al. 2007). A positive stress echocardiogram was associated with a threefold increased incidence of any cardiac event, and a fourfold increased incidence of MI within 12 months of follow-up compared with a negative stress echocardiogram (Krivokapich et al. 1993). Of note, these tests were performed in a population that had a high pre-test probability of developing an MI. While CST may indeed confirm diagnosis in these already symptomatic individuals it would not contribute to the prevention of CAD in this population. Furthermore, the true value of CST in the prevention of CAD lies in the identification of individuals who while at risk, have *not yet* manifested angina. For example, in the Seattle Heart Watch Study, men with 1 risk factor (positive family history, smoking, hypertension [blood pressure >140/90 mmHg], and hypercholesterolemia [total cholesterol >240 mg/dL]) and 2 abnormalities on exercise testing (chest pain, exercise 1.0 mm, or 1 mm of ST depression on exercise testing had a 5.7-times greater risk of death from CAD than those with a negative test. In the Multiple Risk Factor Intervention Trial, retrospective analyses using the ST/HR index found a nearly 4-fold increase in the 7-year rate of death from CAD among men with an abnormal test response and suggested that the exercise ECG might serve to identify high-risk men who do benefit from interventions targeting risk factor reduction. Therefore, in asymptomatic men >40 years of age with 1 risk factor, exercise testing could provide useful information as a guide to aggressive risk factor intervention (Bruce et al. 1980).

In addition to the above, CST may also be useful in measuring the functional capacity of patients with established heart disease. In patients with CAD, CST may help assess the functional significance of partial blockages. If during CST signs of ischemia occur at a low level of exercise, the blockages could be presumed to be very significant and conversely, if ischemia occurs only at high levels of exercise or does not occur at all, the blockages are likely to be much less significant.

The Safety of CST

Major complications of exercise testing include hemodynamic instability, arrhythmia, myocardial infarction and rarely death. The rates of mortality due to CST were from 1.7 to 1 per 10,000 in data collected prior to 1971 (Rochmis and Blackburn 1971). However, over the last three decades, the improvement and standardization of techniques have further reduced the morbidity and mortality associated with CST (Gibbons et al. 2002). Thus, more recent estimates of serious complications (including myocardial infarction and other events

requiring hospitalization) in subjects with and without known disease, is 1-5 per 10,000 tests, with death estimated to occur in ≈ 0.5 per 10,000 tests (Rodgers et al. 2000; Stuart and Ellestad 1980). The reduced morbidity and mortality associated with CST has been attributed to several reasons, some of which have direct relevance to the development of PST including:

1. Identification of absolute and relative contraindications to testing (e.g., acute recent MI, acute myocarditis and pericarditis, uncontrolled cardiac arrhythmia) ;
2. Absolute and relative indications for aborting testing (“stopping rules”) (e.g., ST Segment elevation of more than 1 mm; moderate to severe angina, signs of poor perfusion, e.g., emergence of arrhythmias);
3. Identification and selection of safe stimuli;
4. Standardized procedures for testing;
5. Standardization of necessary safety equipment (e.g., emergency kit of and DC defibrillator) to be available during testing;
6. Standardization of intervention protocols to manage adverse events (reversal with nitroglycerin administration).

Limitations of CST

CST can only facilitate the diagnosis of obstructive CAD, in which the plaques cause significant obstruction to blood flow. However, there could be plaques that do not obstruct blood flow significantly, but could rupture leading to the formation of a thrombus eventually obstructing the coronary artery and leading to an MI. Thus, CAD could also be associated with a “normal” stress test (false negative).

Another major limitation of CST is that for it to be positive, the coronary arteries need to be occluded by 65% or more. This limitation applies to all forms of CST because all the outcomes (EKG, echocardiogram or radio-imaging) still depend upon there being a limitation of blood flow to the myocardium.

What CST Unmasks

CST is based on the principle that application of stress to a compromised system allows a latent abnormality to be revealed. Thus, the application of physical exercise, pharmacological stimulation or both, CST unmasks the *consequence* of plaque formation i.e. coronary hypoperfusion. The latter manifests as physical symptoms and alterations in vital signs and/or EKG and is predictive of MI. CST does not reveal the primary pathophysiology of CAD i.e., plaque, but rather unmasks the consequences of plaques i.e. coronary hypoperfusion. Thus, CST is clinically useful even though it does not reveal the primary pathophysiology of CAD (Fig. 1). By analogy, a stress test designed to unmask the risk for schizophrenia might do so by manifesting the consequences of the underlying pathophysiology without revealing the precise pathophysiology (Fig. 2). This point is important given that the precise pathophysiology of schizophrenia remains elusive and thus,

its elucidation might not be a necessary prelude to developing a screening test that is clinically useful.

Table 3 outlines how CST can inform the development of a potential PST and draws parallels between the stimuli, outcome measures and clinical applications. The proposed stimuli, outcome measures and clinical application of a potential PST are discussed below.

Projected development of stimuli for psychosis stress testing

It is expected that the development and refinement of PST into a clinically useful tool, will be an iterative process. A number of factors should be considered in the development of ideal stimuli for PST (Table 4). The ideal stimulus would be one that confers PST with high sensitivity, specificity, PPV and NPV in identifying individuals at risk. An ideal stimulus for PST should also have the following properties: 1) measurable dose, 2) uniform delivery, 3) good dose-response, 4) repeatability, 5) good test-retest reliability, and 6) good safety and tolerability. Furthermore, a preferred stimulus would be one that is known to be experienced by the population being tested outside of testing conditions – like physical exertion for CST.

Psychosocial stress stimuli e.g., the Trier social stress test (Kirschbaum et al. 1993) and the Montreal Imaging Stress Test (Pruessner et al. 2004) can induce transient psychological stress in healthy subjects as well as patients with schizophrenia and individuals with a family history of psychosis. Such stress paradigms would have great acceptability because the stress induced is modest, transient and well-tolerated. However, these stimuli are difficult to quantify and dose, have limited repeatability and may not elicit a large enough or specific enough response to identify risk of schizophrenia.

Pharmacological stimuli offer some advantages over psychological stimuli such as measurable dose, uniform delivery method, measurable dose-response and repeatability. Ketamine (Krystal et al. 1994; Malhotra et al. 1997; Malhotra et al. 1996; Parwani et al. 2005) delta-9-tetrahydrocannabinol (THC) (D'Souza et al. 2004; D'Souza et al. 2005), dopaminergic agonists (Angrist et al. 1982; Angrist et al. 1980; Laruelle et al. 1995), *m*-Chloropiperazine (Iqbal et al. 1991; Krystal et al. 1993), iomazenil (Ahn et al. 2011), psilocybin (Vollenweider et al. 1998), salvinorin A (Ranganathan et al. 2012) and N,N dimethyltryptamine (Strassman et al. 1994) have been administered to healthy individuals and/or those with schizophrenia. In the few studies that have studied these drugs in populations at risk for psychosis (Abi-Dargham et al. 2004; Egerton et al. 2013; Henquet et al. 2006; Howes et al. 2011), the goal has been to characterize neurotransmitter abnormalities e.g., dopamine agonists to study dopamine function. Hence, thus far, psychological and pharmacological stimuli have been directed towards studying the pathophysiology of schizophrenia and not for the early detection and risk stratification of individuals at risk (D'Souza et al. 1999).

Projected development of outcome measures for PST

Putative stimuli for PST can induce transient mood changes, perceptual alterations and a range of psychosis-like effects (Angrist et al. 1980; Hope et al. 1951; Janowsky et al. 1973; Lieberman et al. 1987; Pennes 1954; Simon and Taube 1946) that can be captured using

self-reported measures such as the Visual Analog Scales (VAS) and the Psychotomimetic State Inventory (PSI) (Mason et al. 2008), and also clinician rated measures such as the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962), Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987) and Clinician Administered Dissociative Symptoms Scale (CADSS) (Krystal et al. 1994). Objective outcomes include cognitive testing (verbal memory, working memory, attention and executive function (Morgan and Curran 2006; Ranganathan and D'Souza 2006), electrophysiological indices of information processing (p50 (Light et al. 1999; Vollenweider et al. 2007), p300 (D'Souza et al. 2012), gamma oscillations (Cortes-Briones et al. 2015a), cortical noise (Cortes-Briones et al. 2015b) and mismatch negativity (Umbricht et al. 2002)) and brain imaging (Positron Emission Tomography (Egerton et al. 2013; Vollenweider et al. 1997; Wolkin et al. 1987), Single Photon Emission Computerized Tomography (Laruelle et al. 1996), functional Magnetic Resonance Imaging (fMRI) (Anticevic et al. 2012; Corlett et al. 2013; Driesen et al. 2013) and Magnetic Resonance Spectroscopy (Stone et al. 2012). While those at risk might show abnormalities in these measures at baseline, a PST might magnify these changes to a level that might help differentiate risk more conclusively. These measures will need to be tested in suitable target populations with a wide range of risk and also for their sensitivity to the proposed stimuli used in PST to determine their suitability as target outcome measures.

The Target Population for PST

An iterative process may be expected in refining the group who would benefit most from a PST. Thus, PST may be most useful in identifying individuals who while at risk, have not yet manifested symptoms of psychosis for which a population with a wide range of risk for schizophrenia would need to be studied. Table 1 lists risk factors that could potentially assist in identification of a population that would benefit from a PST.

Finally, the development of a suitable PST must consider the risk/benefit profile of the approach.

Safety of PST

As with CST, in order for PST to become a clinically useful tool safe stimuli need to be identified, the absolute and relative contraindications to testing, the testing parameters, the indications for aborting testing, and the protocols for managing adverse events need to be operationalized.

That the outcome measures for CST are EKG changes, perfusion abnormalities or chest pain, and *not* myocardial infarction, confers a favorable risk:benefit profile for CST. Similarly the proposed outcome measures for PST would need to be signs or symptoms proximal to full blown psychosis, and not the latter for it to be acceptable. The currently proposed stimuli and outcome measures for PST meet this threshold. Further as discussed above, development of a PST will require identification of parameters and guidelines for termination of testing as well as provision for rescue medications.

A proposed PST Stimulus – for the example of cannabinoids

As an initial step toward identifying a suitable stimulus for PST, taking into account the favorable profile of existing pharmacological stimuli, we suggest that cannabis or its primary active component THC may offer some advantages over others. First, exposure to cannabis is widespread; it is by far the most commonly used illicit drug worldwide especially among young adults, who would be the target population for a PST. For instance, in the U.S., the rate of lifetime exposure to cannabis among twelfth graders is almost 50% (Johnston 2014) and with the increasing legalization of cannabis in the U.S. it is conceivable that the proportion of the population with any exposure to cannabis might increase. Furthermore, the rates of cannabis use in individuals at risk for psychosis are high. For example, in the North American Prodrome Longitudinal Study (NAPLS) 30% of the controls and 40% of the clinical high risk sample rated themselves as current users of cannabis (Addington et al. 2012). Furthermore with the growing legalization of medical and recreational cannabis across the U.S. (Bly 2012; Kleber and Dupont 2012; procon.org), it is conceivable that exposure to cannabis in the population could increase. Thus, the proposed stimulus is one that the target population has likely been exposed to. Second, relevant to psychosis, the recreational use of cannabis has been linked to *transient* psychosis related outcomes i.e., the *stimulus is related to the outcome of interest*. Thus, in laboratory studies cannabinoids (THC and nabilone) can induce acute, transient psychosis related outcomes in healthy subjects and exacerbate psychosis in individuals with schizophrenia (D'Souza et al. 2005; Radhakrishnan et al. 2014). Furthermore, distinct from these acute effects, epidemiological studies suggest an association between cannabis exposure in adolescence and later psychosis outcomes including schizophrenia (Radhakrishnan et al. 2014). Third, related to safety, while not completely without risk, laboratory studies with THC have been well-tolerated and are not associated with psychosis beyond the test day in healthy individuals with and without a family history of psychosis (Henquet et al. 2006) and even in patients with established schizophrenia (D'Souza et al. 2005). In a review of the safety of THC in controlled laboratory conditions in 266 subjects, there was one serious and 70 minor adverse events in 9.7% of subjects. Nausea and dizziness were the most frequent side effects. Of 149 subjects on whom long-term follow-up data (up to one year) were gathered, 94% reported either no change or a reduction in their desire to use cannabis in the post-study period (Carbuto et al. 2012b). The effects of THC or cannabis have also been studied in individuals with psychosis liability as defined by a family history of psychosis or psychometrically (a threshold score on the Schizotypal Personality Questionnaire) (Henquet et al. 2005; Henquet et al. 2006; Verdoux et al. 2003). It is reasonable to assume that the acute risks of a PST in individuals at risk for psychosis will fall somewhere in between healthy individuals and individuals with an established psychotic disorder. Thus, the most likely risks of PST observed in healthy adults and adults with psychotic disorders or risk of psychosis, are transient, and spontaneously reversible psychotic symptoms (not disorder), anxiety, and cognitive deficits. This begs the question, are the risks of CST comparable to the risks of PST? For example, how do the risks of a commonly used pharmacological cardiac stress test, the dobutamine stress test compare to the effects of THC in the laboratory. According to the AHA “complications of dobutamine infusion include nausea, headache, tremor, anxiety, angina and atypical chest pain, atrial and ventricular arrhythmias,

and hypertension or hypotension. MI ($<0.02\%$) and death ($<0.002\%$) as complications are very rare". As compared to this, during THC infusions, we have encountered minor side effects such as nausea and headache in $< 2\%$ subjects (Carbuto et al. 2012a) and hypertension in one subject with pre-existing hypertension. Fourth, THC offers advantages over psychological stressors in having greater specificity in inducing psychosis-relevant outcomes in addition to possessing repeatability, test-retest reliability, uniform dosing and predictable dose-response. A comparison of THC with other putative pharmacological stimuli is presented in Table 4.

Existing data on THC suggest that it could possess an acceptable risk benefit profile as a PST stimulus. While most existing data is on THC-induced behavioral effects, recent studies have examined its effects on schizophrenia-relevant electrophysiological and neurocognitive biomarkers. For example, THC has been shown to reduce P300 amplitude (D'Souza et al. 2012), auditory mismatch negativity (Juckel et al. 2007), disrupt gamma oscillations (Cortes-Briones et al. 2015a) and increase cortical noise (Cortes-Briones et al. 2015b) measured in EEG. The use of such biomarkers may permit developing a PST using a dose of THC low enough to minimize significant distress. Further testing may help determine contra-indications for PST e.g., individuals with existing acute psychotic symptoms, past history of severe psychotic reactions etc. "Stopping rules" for PST need to be operationalized and may include an increase in psychosis-like symptoms beyond a predetermined threshold (e.g., $>30\%$ PANSS score increase) and/or in subjective distress. Rescue procedures (e.g., lorazepam; extended observation) will need to be operationalized.

The acceptance of PST

For PST to be of any value, it would need to be done before or during the window of vulnerability. The latter is typically from adolescence to young adulthood. Society has much lower thresholds of what is unacceptable in adolescents vs. adults. Interestingly, while cardiac stress testing is *typically* done in adults it may not be well known that it is also routinely used in children too, for the evaluation of cardiac disease (Ghosh et al. 2015; Washington et al. 1994). The American Heart Association (AHA) has a position statement about stress testing in children and adolescents (Paridon et al. 2006) with 1) guidelines for how to obtain consent for CST from the parent and assent from the child, 2) Equipment requirements, 3) Indications and Contraindications for Stress Testing, 4) Indications for Exercise Testing Termination, and 5) Protocols for testing. While there is limited data on the safety of CST in children and adolescents, it is not devoid of clinical significant risks including arrhythmias and in theory, death.

The acceptance of a PST will depend on the benefit realized by earlier discovery of a psychotic disorder, balanced by any negative consequences. Furthermore, the value of a PST will depend on the effectiveness of the existing treatment interventions. Having curative treatments would make the value of a PST very high. However, curative treatments for psychotic disorders do not exist. In fact, there are few curative disorders for most chronic medical and psychiatric conditions. In some instances, as is the case with Alzheimer's Disease (AD), while existing treatments do not change the ultimate course of the disease, some approaches could slow the process of AD, especially when used early in the course of

the disease. Or in the case of psychotic disorders, managing psychosis with antipsychotics drugs can alter outcome through a number of pathways without necessarily altering the pathophysiology of the disorder. Detecting a psychotic disorder earlier may provide the impetus to develop treatments that arrest or slow the disease process beyond what is offered by existing antipsychotic treatment. Finally, PST may be more acceptable and justified if the stressor stimulus is one that is commonly encountered by many people similar to physical exertion and CST.

The feasibility and acceptance of screening of children and adolescents for other disorders is relevant to the development of a psychosis stress test. The World Health Organization commissioned Wilson and Jungner (1968) to develop criteria to guide the selection of conditions that would be suitable for screening tests. The criteria have been challenged, and revised; and are presented (table: 5) to provoke discussion about how these apply to PST. Applying these criteria for PST, there is enough to make the case for developing and testing a PST as a screening tool for psychotic disorders.

Pitfalls of Psychosis Stress Testing

The most significant problems associated with any screening test are the problems of false positives and negatives, which PST will undoubtedly be associated with. In fact, the adverse effects from false positive or false negative test results with cardiac stress testing for coronary artery disease is estimated to have a greater negative impact than the risks associated with the tests themselves (Arbab-Zadeh 2012). If 25% of those who are false positive undergo cardiac catheterization, they would be exposed to the chance of a major complication (1.7%) including myocardial infarction, stroke, or even death. If a person is wrongly diagnosed (false positive) with a psychotic disorder, he/she may be subjected to unnecessary stigma, shame and treatment. The individual and the family may have to endure unnecessary stress caused by the belief (erroneous) of having a life-long, incurable disorder. A false negative result could give rise to a false sense of security and treatments that could alter disease course could be delayed. The rates of false positive and negative cases of a psychotic disorder will only become evident with time.

Challenges

While there are numerous attractive possibilities in applying lessons learned from CST to the detection of risk for or conversion to psychosis, there are several limitations that need to be acknowledged and taken into account in the development of PST.

First, if schizophrenia is an assortment of disorders caused by varying pathophysiologies that is currently viewed as a single disorder, it is possible that a single stimulus/test will not have sufficient sensitivity or specificity. Nevertheless, as discussed earlier, if there is some final common pathway to the expression of ischemia then CST is useful regardless of the primary pathophysiology i.e., plaque, vasospasm or inflammation. Extrapolating this to psychotic disorders, if there is some common final pathway to psychosis, then regardless of the different primary pathophysiologies (as yet unknown), PST might still be useful.

Second, the lifetime prevalence of CAD has been estimated by the Centers for Disease Control to be 6% while the lifetime prevalence of schizophrenia is lower. Thus, the PPV of any PST is likely to be low. However, it should be noted that the estimated prevalence of CAD in those aged 18-44 years by the CDC is 1.2% - comparable to schizophrenia. Furthermore, if a PST is to screen for psychotic disorders in general including Bipolar Disorder and Schizoaffective disorder, then the cumulative rates of these disorders is even higher.

Third, “state” factors such as recent stress, fatigue, insomnia, anxiety and substance use may influence the outcome measures on the PST and lead to false positives. However, similar factors may apply to CST but have not negated its usefulness. Fourth, vulnerable individuals who might be candidates for PST, may have a greater incidence of mood and anxiety disorders, substance use and personality disorders even in the absence of a psychosis, all of which could impact the outcomes of the PST.

Conclusions

The history of evolution of CST may guide the development of a similar approach for the detection and management of psychotic disorders. Current approaches for detecting the risk for or conversion to psychosis in high-risk individuals rely on the presence of attenuated positive symptoms which is analogous to diagnosing CAD *after* the occurrence of angina or MI. Similar to CST, the initial development of a test to unmask latent risk for schizophrenia will require the selection of a suitable and safe stimulus and the development of outcome measures as a prelude to testing in populations with a range of risk to determine predictive value. The use of CST in CAD offers the intriguing possibility that a similar approach may be applied to the detection and management of schizophrenia.

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Figure 1.
Cardiac Stress Testing

Figure 2.
Proposed Psychosis Stress Testing

Table1

Levels of prevention in schizophrenia

	General population	Populations at high risk	Populations at high risk manifesting sub-threshold symptoms	Schizophrenia and other psychotic disorders
Universal	Vitamin D “prophylaxis” (McGrath et al. 2010) Improved obstetric care (McGrath 2000) Improved prenatal nutrition and infection control (McGrath 2000) Substance abuse prevention: cannabis and amphetamines			
Selective (we propose that a psychosis stress test could identify at risk individuals at a stage where selective interventions would be effective)		Non-pharmacological interventions in children with social skill deficits / anxiety / depression Screening tools for risk stratification Active monitoring and follow-up Intervention to treat substance abuse (Hickman et al. 2009)		
Indicated			Omega 3 fatty acids (Amminger et al. 2010) Antipsychotic medications (McGlashan et al. 2006) Treatment of sub-threshold or prodromal symptoms with antidepressants Supportive psychotherapy and family interventions (Bechdolf et al. 2012) Cognitive therapy (Morrison et al. 2002; Morrison et al. 2007)	

Table 2

Biobehavioral models of predicting schizophrenia

Reference	Subjects	Parameters	Duration of follow-up	Outcome	Statistical model	Sensitivity (sens) Specificity (spec) PPV NPV
Cannon et al. (1990)	207 first degree relatives of schizophrenia 104 matched controls	Delivery complications Autonomic responsiveness Rearing environment Skin conductance School behavior Father's diagnosis	10 years	Negative symptom schizophrenia / Positive symptom schizophrenia	Decision tree and logistic regression tree	PPV for negative symptom schizophrenia in HR children with delivery complications + autonomic non-response –86% PPV for positive symptom schizophrenia in HR children with delivery problems + disruption of learning environment – 40%
Klosterkötter et al. (1997)	96 patients with DSM-111-R diagnoses of personality disorders	Subjective experiences of neuropsychological deficits using standardized instruments	8 years	Presence or absence of schizophrenia		In 77% of cases the outcome 'schizophrenia vs. no schizophrenia' was correctly predicted by the earlier presence or absence of self-experienced disturbances of thought, speech, memory, perception and action
Davidson et al. (1999)	Data of the national psychiatric hospitalization registry (individuals hospitalized with a diagnosis of schizophrenia between 1970 and 1995, (n=509) linked to the data in the national psychiatric registry (9215)	Intelligence Social functioning Organizational ability Interest in physical activity Individual autonomy	4-10 years	The patients with schizophrenia (n=509) got worse scores on intelligence, social functioning and organizational ability as compared to the non-patients in the national psychiatric registry (n=9215)	Conditioned logistic regression analysis	In the analysis of patient vs. non-patients the three factors combined correctly predicted a patient outcome with sens – 75%, spec – 100% PPV – 72% When the model was applied to the draft board registry Sens – 74.7% Spec – 99.7% PPV – 42.7%
Klosterkötter et al. (2001) Schultze-Lutter et al. (2006)	Patients referred to outpatient clinics of German University department	Basic symptoms Cognitive-perceptive basic symptoms (COPER) Cognitive basic symptoms	9.6+7.6 years	schizophrenia		BS: sens – 0.98; spec – 0.59; PPV – 0.70; NPV – 0.96 COPER: sens – 0.87; spec – 0.54; PPV – 0.65; NPV

Reference	Subjects	Parameters	Duration of follow-up	Outcome	Statistical model	Sensitivity (sens) Specificity (spec) PPV NPV
	ts for diagnostic problems	(COGDIS)				– 0.82 COGDIS: sens – 0.67; spec – 0.83; PPV – 0.79; NPV – 0.72
(Carter et al. 2002)	212 Danish subjects with one parent with schizophrenia or a schizophrenia spectrum disorder 99 matched subjects with no such parent	25 premorbid variables in seven domains genetic risk birth factors autonomic responsiveness cognitive functioning rearing environment personality school behavior	25 year follow-up	32 / 212 and 1/99 got a diagnosis of schizophrenia a multiplicative interaction effect of genetic risk × rearing environment × disruptive school behavior	Discriminant function analysis (schizophrenia Vs no mental illness) (schizophrenia Vs non-schizophrenia outcome)	PPV-60%
Eack et al. (2008)	First degree relatives of schizophrenia patients (n=66), second degree relatives (n=20)	Cognitive tests (WAIS WCST, SWMT) Prodromal symptoms (PAS, MIS, SAS), K-SADS Brain MRI	3 years (± 1.13)	71% chance that the identified individual would develop any psychopathology	Structural equation modeling	Sens – 50% Spec – 92% PPV – 71%
Cannon et al. (2008)	291 subjects at clinical high risk	Genetic risk, deterioration in functioning, unusual thought content, suspicion paranoia, substance abuse	Q 6 months to 2.5 years	Psychosis	Cox proportional hazards multivariate cox regression	Sens– 0.10-0.67 Spec– 0.84-0.97 PPV = 0.46-0.81/NR
Riecher-Rössler et al. (2009)	Fifty-three ARMS subjects	attenuated psychotic symptoms (suspiciousness), negative symptoms (anhedonia/asociality), and cognitive deficits (reduced speed of information processing)	Upto seven years	psychosis	Predictive variables were selected with the backward elimination algorithm with logistic regression. Initially, the full model contained all nonredundant domain variables and then, variables were excluded step by step if they did not sufficiently contribute to the prediction of psychosis.	With these predictors in an integrated model for predicting transition to psychosis, the overall predictive accuracy was 80.9% with a sensitivity of 83.3% and a specificity of 79.3%.
Koutsouleris et al. (2009)	The first classification analysis - 20 early and 25 late at-risk and 25 HCs. The second	Multivariate neuroanatomical pattern classification was performed on the structural MRI data of individuals in early or late ARMS	Four years	psychosis	The predictive power Was evaluated by categorizing the baseline imaging data of individuals with transition to psychosis vs those without transition vs HCs.	HC vs ARMS-E Sens- 95% Spec- 80% PPV- 79% NPV – 95% ARMS-E vs ARMS-L Sens- 84% Spec- 80% PPV- 84%

Reference	Subjects	Parameters	Duration of follow-up	Outcome	Statistical model	Sensitivity (sens) Specificity (spec) PPV NPV
	analysis - 15 individuals with transition, 18 without transition, and 17 HCs.	vs healthy controls (HCs).				NPV – 80% HC1 vs ARMS-L Sens- 76% Spec- 80% PPV- 79% NPV – 77%
Zimmermann et al. (2010)	Thirteen ARMS patients with later transition to psychosis (ARMS-T) and fifteen without (follow-up period of at least 4 years) (ARMS-NT)	spectral resting EEG data (of 8 electrodes over the fronto-central scalp area placed according to the 10–20 system) and summary score of the Scale for the Assessment of Negative Symptoms (SANS).	Upto 7 years	psychosis	SANS score in combination with power in the delta, theta, beta1, and beta2 bands, respectively, predicted transition significantly (pb.03)	Delta power * neg symptoms Sens- 0.92 Spec- 0.73 PPV – 0.75 NPV – 0.92 Theta power * neg symptoms Sens- 0.92 Spec- 0.87 PPV- 0.86 NPV – 0.93
Ruhrmann et al. (2010)	245 subjects clinical high risk, basic symptoms	Positive symptoms, bizarre thinking, sleep disturbance, schizotypal disorder, level of functioning, years of education	Q 9 months till 1.5 years	psychosis	Cox proportional hazards multivariate cox regression	Sens– 0.42-0.68 Spec– 0.46-0.98 PPV = 0.24-0.83 NPV – 0.85-0.87
Thompson et al. (2011)	Clinical high risk	Unusual thought content, low functioning, genetic risk	2.33 years	Psychosis	Cox proportional hazards multivariate cox regression	Sens- 0.17-0.37 Spec- 0.87-0.94 PPV - 0.63-0.67 NPV – 0.63-0.68
Dragt et al. (2011)	Clinical high risk, basic symptoms	Baseline combinations of urbanicity, socio-sexual aspects and personal adjustment	9, 18, 24, 36 months	Psychosis	Cox proportional hazards multivariate cox regression	Sens– 0.5-1 Spec– 0.69-0.92

Reference	Subjects	Parameters	Duration of follow-up	Outcome	Statistical model	Sensitivity (sens) Specificity (spec) PPV NPV
Koutsouleris et al. (2011)	Pairwise and multigroup biomarkers were constructed using the MRI data of 22 healthy volunteers, 16/21 at-risk subjects with/without a subsequent disease conversion.	MRI-based classification system in predicting disease conversion	Upto seven years	Psychosis as per transition criteria described by Yung et al.	neuroimaging-based multivariate pattern recognition algorithms-support vector machine (SVM) to generate MRI based classification	HCvs converters = 92.3% HC vs nonconverters = 66.9% converters vs nonconverters = 84.2%, converters vs nonconverters = likelihood ratio 6.5
Shah et al. (2012)	96 young first- and second-degree relatives of schizophrenia probands	familial, neurobiological, socioenvironmental, cognitive and clinical domains	Followed up for an average of 2.38 (SD=0.98) years	psychosis	Iterative structural equation modeling	Sens- 0.17 Spec- 0.99 PPV- 0.67 NPV - 0.89.
Nieman et al. (2013)	61 subjects at clinical high risk	Prognostic score composed of premorbid social adjustment and P300 oddball task	36 months	29% converted to psychosis	cox proportional hazard modeling	The prognostic score showed sens - 88.9% spec- 82.5%. 3 risk classes establishing a prognostic index. In the class with the worst social-personal adjustment and lowest P300 amplitudes, the PPV was 74%
Michel et al. (2014)	97 subjects at clinical high risk	Prediction model comprised of at-risk criteria (attenuated psychotic symptoms plus subjective cognitive disturbances) and a processing speed deficit (digit symbol test).	24 months	psychosis		hazard rates between 0.0 (both predictors absent) and 1.29 (both predictors present)
Perkins et al. (2014)	Clinical high risk individuals who developed psychosis (CHR-P) (n=32) who did not	expression of plasma analytes reflecting inflammation, oxidative stress, hormones, and metabolism	2 years	psychosis	A "greedy algorithm" that selected analytes that best distinguished persons with CHR-P from UC and from CHR-NP	The classifier included 15 analytes (selected from 117), with an area under the receiver operating curve for CHR-P vs UC of 0.91 and CHR-P vs CHR-NP of 0.88.

Reference	Subjects	Parameters	Duration of follow-up	Outcome	Statistical model	Sensitivity (sens) Specificity (spec) PPV NPV
	develop psychosis (CHR-NP) (n=40) and unaffected individuals (UC) (n=35)					
van Tricht et al. (2014)	113 CHR subjects	QEEG spectral power and alpha peak frequencies	18 months	psychosis	Cox regression yielded a model including frontal theta and delta power, and occipital-parietal alpha peak frequencies as predictors of conversion to psychosis. The resulting equation enabled the development of a prognostic index with three risk classes	Hazard rates for class I = 0.057; class II = 0.160; class III = 0.810
Schultze-Lutter et al. (2014)	246 attendees at a early detection of psychosis clinic	Ultra high risk and COGDIS	48 months, naturalistic	psychosis	Kaplan-Meier survival analysis to calculate hazard rates	The 48-month hazard rates for were: only COGDIS 0.23; only UHR 0.28; COGDIS + UHR 0.66.

Positive Predictive Value (PPV): number of true positive / number of positive test results

Negative Predictive Value (NPV): number of true negative / number of negative test results

Specificity: number of true positives / true positives + false negatives (actual number of affected individuals)

Sensitivity: number of true negatives / true negatives + false positives (actual number of unaffected individuals)

Table 3

Parallels between Cardiac and Psychosis Stress Testing

	Cardiac Stress Test	Proposed Psychosis Stress Test
Stressor	<i>Physical Exercises:</i> Sit-ups, Running up and down the stairs (historical), Bruce protocol <i>Pharmacological:</i> Dobutamine, Dipyridole, Adenosine	<i>Social/Cognitive exercises:</i> Trier stress test Montreal Imaging Stress test Self-reported stress (historical) <i>Pharmacological:</i> Amphetamine, PCP, ketamine, THC
Outcome measures	<i>Self-reported:</i> Chest pain, SOB, palpitations <i>Clinician-rated:</i> none <i>Objective:</i> Heart rate, blood pressure, changes in EKG, <i>Imaging Outcomes:</i> Blood flow measured using ECHO, Coronary perfusion studies (Thallium scan)	<i>Self-reported:</i> Changes in perception, mood and thought content and process <i>Clinician-rated:</i> Changes on Rating scales to measure psychosis, mood, cognitive performance <i>Objective:</i> Electroencephalography <i>Imaging outcomes</i> Blood flow using fMRI; neurochemistry using MRS; SPECT Neuroreceptor imaging with PET: FNIR (functional near infrared optical imaging)
Clinical application a) Risk assessments and early diagnosis b) Target population c) Contraindications Benefits / utility Risks	CAD Individuals at risk for CAD on the basis of demographics, history, physical examination, laboratory assessments and EKG Absolute contraindications include acute MI, unstable angina not previously stabilized by medical therapy, uncontrolled cardiac arrhythmias, severe obstructive valvular lesions Early diagnosis of coronary occlusion and early intervention for primary / secondary prevention and treatment of CAD Arrhythmia, syncope, angina, MI, death	Psychotic disorders Individuals at high risk for psychosis on the basis of family history of psychosis, attenuated psychotic symptoms or schizotypy score high on at-risk measurement scales. Pre-existing psychotic illness. More will need to be identified with the development, experience and refinement of this approach. Early diagnosis of the risk for psychosis and early intervention for primary prevention of psychosis. Transient: anxiety, psychotic symptoms, cognitive impairment, mood changes Persistent: psychosis

Table 4

Characteristics of pharmacological agents as putative stressors for psychosis stress test

Parameter	Amphetamine	Ketamine	THC	Iomazenil	Psilocybin
Epidemiological relationship to psychosis	++ (Amphetamine induced psychosis being re-diagnosed as schizophrenia) (Niemi-Pynttari et al. 2013)	Not established, some emerging evidence of chronic psychosis (Liao et al. 2011)	+++ Cannabis-induced psychosis; Longitudinal studies showing association of heavy persistent cannabis use with schizophrenia. (Radhakrishnan et al. 2014)	Not established	Not established
Acute effects in healthy individuals	↑Positive symptoms (Angrist and Gershon 1970)	↑Positive, negative and cognitive symptoms (Krystal et al. 1994)	↑Positive, negative and cognitive symptoms (D'Souza et al. 2004)	Little or no increase in positive symptoms (Ahn et al. 2011)	Alterations in mood, thought, perception and self-experience (Studerus et al. 2011)
Acute effects in schizophrenia patients	↑Positive symptoms (Angrist et al. 1980)	↑Positive, negative and cognitive symptoms (Lahti et al. 2001; Malhotra et al. 1997; Malhotra et al. 1996)	↑Positive, negative and cognitive symptoms (D'Souza et al. 2005)	↑very small increase in positive symptoms (Ahn et al. 2011)	Not done
Duration of peak effects (minutes)	20 (bolus dose)	Brief: limited by duration of infusion (bolus and constant infusion)	30-60 min (infusion ranged from 2-20 minutes)	10 minutes (infusion over 10 minutes)	4-6 hours
Test-Retest Reliability of acute effects	Good	Good	Good	Good	Good
Dose relationship of acute effects	Good	Good	Good	Good	Good
Standardization of dose and delivery	Good	Good	Good	Good	Good
Adverse effects	Cardiac risks – increased BP/HR, arrhythmias.	Nausea / vomiting Symptom related distress (Carpenter 1999; Lahti et al. 1995)	Nausea, vomiting, tachycardia, anxiety (Carbuto et al. 2012b)	Anxiety, lowered seizure threshold	Anxiety and panic-like reactions
Exposure of general population to the stimulus / recreational use of stimulus	low	low	High (over 50% over 12 th graders)	Low to none	low

Table 5**Criteria for a Screening Test**

Criterion	As applied to PST	
The condition sought should be an important health problem	+	Psychotic disorders are widely recognized as amongst the most debilitating of conditions
The screening program should respond to a recognized need	+	There is growing awareness of the need for earlier detection
There should be accepted treatments for those with the disorder	+	The existing treatments exist but are not curative. Earlier detection may provide the stimulus for developing disease modifying treatment.
The objectives of screening should be defined at the outset	+	To detect as early as possible
There should be a recognizable latent or early symptomatic state	+	A prodrome is well recognized
Facilities for diagnosis and treatment should be available	+	There remains a need for wider access to mental health treatment
There should be a suitable test	?	Still in development
The test should be acceptable to the population	?	Acceptance will need to be gauged while the test is in development
There should be a defined target population.	?	PST might be more appropriate to conduct in high risk populations rather than universal screening
The natural history of the condition, including development from latent to declared disease, should be adequately understood	+	The course of psychotic disorder is generally understood but the conversion from latent to declared disease is not well understood.
There should be scientific evidence of screening program effectiveness.	–	While not currently available, this would become so as PST is tested.
The program should integrate education, testing, clinical services and program management.	+	Specialized clinics for those recently diagnosed with a psychotic disorder include these elements.
There should be quality assurance, with mechanisms to minimize potential risks of screening.	?	Could be developed
The program should ensure informed choice, confidentiality and respect for autonomy.	+	
The program should promote equity and access to screening for the entire target population.	?	This would be easier to do in nationalized health systems
Program evaluation should be planned from the outset.		Could be developed
The overall benefits of screening should outweigh the harm.	Not clear	Needs to be determined
There should be an agreed policy on whom should be treated	?	To be developed
The cost of case finding should be economically balanced in relation to possible expenditure on medical care as a whole	?	To be assessed. In the long run, early discovery may result in lower direct and indirect costs of disease burden
Case finding should be a continuing process and not a “once and for all” project	+	

(Adapted from the World Health Organization, 1968)