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Four reasons why early detection centers for psychosis should be renamed and their treatment targets reconsidered: we should not catastrophize a future we can neither reliably predict nor change

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Abstract

Since the 1990s, facilities for individuals at putative risk for psychosis have mushroomed and within a very short time have become part of the standard psychiatric infrastructure in many countries. The idea of preventing a severe mental disorder before its exacerbation is laudable, and early data indeed strongly suggested that the sooner the intervention, the better the outcome. In this paper, the authors provide four reasons why they think that early detection or prodromal facilities should be renamed and their treatment targets reconsidered. First, the association between the duration of untreated psychosis and outcome is empirically established but has become increasingly weak over the years. Moreover, its applicability to those who are considered at risk remains elusive. Second, instruments designed to identify future psychosis are prone to many biases that are not yet sufficiently controlled. None of these instruments allows an even remotely precise prognosis. Third, the rate of transition to psychosis in at-risk patients is likely lower than initially thought, and evidence for the success of early intervention in preventing future psychosis is promising but still equivocal. Perhaps most importantly, the treatment is not hope-oriented. Patients are more or less told that schizophrenia is looming over them, which may stigmatize individuals who will never, in fact, develop psychosis. In addition self-stigma has been associated with suicidality and depression. The authors recommend that treatment of help-seeking individuals with mental problems but no established diagnosis should be need-based, and the risk of psychosis should be de-emphasized as it is only one of many possible outcomes, including full remission. Prodromal clinics should not be abolished but should be renamed and restructured. Such clinics exist, but the transformation process needs to be facilitated.

> Personal Assessment and Crisis Evaluation (PACE) works with young people who might be at risk of developing psychosis. By identifying people who are at risk of psychosis and providing them with appropriate treatment, it is hoped that early symptoms will be reduced, while also delaying or perhaps preventing the development of mental health problems.
>
> – PACE website, 3 November 2018

Introduction

Primum non nocere ('first, to do no harm'), derived from the Hippocratic Oath, represents the guiding principle in medicine. Yet, in the presence of unambiguous and highly predictive risk factors for a serious or life-threatening disorder, it is useful to consider treatment of not yet affected individuals to prevent the transformation of a liability into a full-blown disorder, even though adverse events might occur. Starting in the early 1990s (Birchwood and MacMillan, 1993; McGorry *et al.*, 1996), consideration of the cornerstones of responsible therapeutic action – reduction of symptoms as well as prevention of harm – led to the establishment of early detection centers or prodromal clinics for individuals at putative risk of psychosis, such as the Personal Assessment and Crisis Evaluation center (PACE; see quote above). This trend built upon a number of empirical studies, often published in top-tier journals that have greatly changed the way we look upon psychosis today (Malla *et al.*, 2016). For example, schizophrenia is now regarded as a disorder that is preventable and amenable to change – much in contrast to earlier (somatic) models claiming that psychosis is incomprehensible and chronic (Jaspers, 1963). Although this constituted a significant and valuable paradigm shift at the time, the empirical situation that initiated and accompanied the emergence of

the psychosis high-risk concept has since changed. However, significant corrections in how these centers are named and their role in treatment have not been undertaken.

The evidence that led to the early intervention paradigm

Before we formulate our concerns against the early intervention paradigm and facilities for individuals at risk for psychosis,[1] we first provide a brief overview of the rationale and key arguments for early detection and intervention. We also wish to emphasize that we have no doubts about the probity of the researchers who advocated early detection and treatment. In addition, many of the relevant research studies were of excellent quality. Yet, we do criticize the taking of scattered empirical findings as facts, promoting the widespread establishment of early detection centers worldwide.

To clarify, early intervention can mean two things (Marshall and Rathbone, 2011). The term is used to describe treatment for individuals (mainly adolescents and young adults) in the early stages of manifest (and diagnosed) psychotic disorders, but it also refers to therapeutic efforts to prevent the eventual transition into psychosis in individuals with prodromal symptoms. Our article is directed at the latter, although insights from first episode research, especially studies pertaining to the duration of untreated psychosis (DUP), played an important role in justifying intervention with individuals at (putative) risk for psychosis.

One of the strongest arguments (Birchwood and MacMillan, 1993; McGorry *et al*., 1996) in favor of early detection is that the DUP is a predictor of a more severe course of the illness (Marshall *et al*., 2005) and that the best therapeutic window for antipsychotic intervention is the very early phase of psychosis (Perkins *et al*., 2005). Correlations between DUP and outcome were medium to strong in the early studies. In a seminal paper by McGorry *et al*. (1996), the DUP was able to explain 15% of the variance in later quality of life, and this rose to 24% when the duration of the prodrome was added (p. 314). Thus, the idea emerged that early treatment might mitigate the course of the illness or even prevent a transition into psychosis.

Two major paradigms are implemented in the detection of a high risk for psychotic disorders. The ultra-high-risk (UHR) approach focuses on the presence of attenuated (subsyndromal) or brief positive symptoms or on genetic vulnerability accompanied by functional decline. In Germany and central Europe, the presence of basic symptoms (BS) is often used as an additional criterion for a high risk of psychosis. The latter approach considers subjective disturbances of perception, cognition, and language that may not be observable by others yet are experienced by the individual as a stressful departure from their 'normal' state (Andreou *et al*., 2019). It has been suggested that basic symptoms manifest at an earlier prodromal stage of psychosis than UHR symptoms (Klosterkötter *et al*., 2011). However, there are no studies on the comparative predictive validity of the two approaches. A meta-analysis does suggest that brief limited intermittent psychotic symptoms (BLIPS) have greater predictive power than attenuated psychotic symptoms (APS; Fusar-Poli *et al*., 2016*a*).

[1]We are not the first to criticize such facilities. For articles with a somewhat different focus, see, for example, Ajnakina *et al*. (2019) and Conrad *et al*. (2017). Our article repeats a number of arguments made in prior critical reviews (e.g. van Os and Guloksuz 2017), but we focus on the detrimental effects of diagnosis stigma and the multiple methodological problems (e.g. low content and predictive validity and proneness to response biases) of the instruments designed to assess ultra high risk.

The probability of a high-risk individual developing overt psychotic symptoms has been estimated at about 25% in the first 3 years from a diagnosis of the high-risk state and about 35% overall (Fusar-Poli *et al*., 2015; Schmidt *et al*., 2015). Because a high proportion of high-risk individuals will never experience a psychotic disorder, treatment with antipsychotics is usually discouraged by guidelines (Schmidt *et al*., 2015), although exceptions are common in both research (van der Gaag *et al*., 2013) and clinical practice (Nieman *et al*., 2009).

The decline effect

As mentioned, the empirical situation pertaining to high-risk research has changed in recent years, and some predictive associations that are at the heart of the early intervention paradigm have become weaker. This development is likely owing to a phenomenon called the 'decline effect' (Lehrer, 2010) and is not unusual in science. Initial results are often stronger than follow-up findings, which replicate the effect to a much lesser extent if at all. We present four arguments for why psychosis high-risk centers (i.e. for 'future patients') should be relabeled and its treatment targets reconsidered.

Fear of psychosis may increase the likelihood of depression and promotes suicidality

Many prodromal clinics emphasize that their goal is to delay and perhaps even prevent psychosis (see quote at the beginning of the article) and name a number of unspecific symptoms (some more general, some attenuated positive symptoms) that indicate such a risk. However, most people with these symptoms will not develop psychosis. Although 'risk calculators' have been developed to increase predictive accuracy (Cannon *et al*., 2016; Fusar-Poli, 2017), these are based on retrospective group data and have not been readily validated for predictive purposes. Hence, some authors have suggested rethinking risk prediction based on dynamic modeling derived from moment-by-moment assessments (Nelson *et al*., 2017).

The prevalence of suicidal ideation, lifetime self-harm, and lifetime suicide attempts is high in people at putative risk for psychosis (Taylor *et al*., 2015), and the risk of lifetime suicidality is elevated even in non-help-seeking subclinical individuals who experience psychotic-like experiences (Gawęda *et al*., 2019). Nicolas Rüsch and others (Corcoran *et al*., 2010; Rüsch *et al*., 2014) posed an important question that is implicit in this article: 'Are labeling and stigma an acceptable price to pay for early intervention?' (p. 487). According to an emerging trend in studies, the prospect of later psychosis induces fear, hopelessness, self-stigma, and demoralization as well as a feeling of being 'damaged' (Corcoran *et al*., 2005; Yang *et al*., 2013). Stigma, stigma stress, and fear of deterioration are predictors of suicidality (Pompili *et al*., 2007; Ventriglio *et al*., 2016; Xu *et al*., 2016). According to Ventriglio and colleagues (2016), early insight may induce a change in an individual's self-image from that of a healthy person to an ill person, and this may be one reason why many clinicians do not inform their patients of the diagnosis of schizophrenia (Villani and Kovess-Masféty, 2017), even if it is undisputed. There is early evidence that stigma may even increase the risk of transition to psychosis. In a prospective study of 171 young persons at risk for psychosis, Rüsch and colleagues (2015) showed that perceived harm due to stigma at baseline was associated with a higher risk of transition to psychosis after one year, even

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when controlling for baseline symptom severity and functioning. According to another recent study (Miegel *et al.*, 2019), 'fear of becoming psychotic' is prevalent in many patients with obsessive-compulsive disorder (OCD; 32.1%) or depression (20.4%) and is significantly associated with suicidality at a medium effect size. This association is unlikely to disappear in the near future since the stigma of schizophrenia has increased rather than diminished over the past decades (Schomerus *et al.*, 2012; Angermeyer *et al.*, 2013).

To summarize, a strong emphasis on the (relatively low) possibility of schizophrenia (with the best of intentions) may unintentionally foster the development of a psychiatric disorder. This may be caused by an induction of rumination/worry, which represents a prominent transdiagnostic facilitator of prospective mental problems *per se* (Aldao and Nolen-Hoeksema, 2010).

Longer duration of untreated psychosis (DUP) is weakly correlated with poor outcome

As noted, evidence in favor of a connection between DUP and outcome in schizophrenia and an inverse association between DUP with a response to antipsychotic intervention seemed persuasive in early research but began to crumble after only a short time. As early as 2001, Ho and Andreasen (2001) cast doubt on the connection in light of evidence collected in 2000. Meta-analytic data now show that the DUP is significantly associated with outcome (sometimes with positive symptoms, sometimes with negative symptoms; Penttilä *et al.*, 2014), but the connection is weak to very weak (lower than $r = 0.2$ for all major parameters, thus explaining less than 4% of the variance). Importantly, we still do not know whether the DUP is a primary factor or an epiphenomenon. Whether the duration of the untreated prodrome (McGorry *et al.*, 1996), clearly the most relevant parameter, is associated with the outcome is even more elusive since only few studies have addressed this (Polari *et al.*, 2018; Rosengard *et al.*, 2019).

Problems with concurrent and predictive validity of risk factors

As highlighted by Jim van Os and others (van Os and Guloksuz, 2017; Guloksuz and van Os, 2018), the criteria for transition are often vague. This, in turn, burdens replication. Identification of at-risk individuals also seems to be inflated by recruitment strategies, known as risk enrichment; the pretest risk for psychosis at 38 months was 15% in help-seeking samples selected for clinical high risk (CHR) assessment compared to 0.1% in the general population (Fusar-Poli *et al.*, 2016*b*). Van Os also notes that transition rates reported in earlier studies (40%) have more than halved (15%) over the years (Guloksuz and van Os, 2018). This may have resulted from indiscriminate application of high-risk criteria to populations with low pretest risk, due to the publicity that the concept has received (Guloksuz and van Os, 2018). CHR is a weak predictor of later psychosis. A recent meta-analysis (Beck *et al.*, 2019) shows that many individuals with CHR do not experience remission from the symptoms and display a clinical diagnosis at follow-up – mainly mood and anxiety disorders but not psychosis (see also Michel *et al.*, 2018) – and that approximately half show a poor psychosocial outcome (for compatible findings see Lin *et al.*, 2015).

Further, assessment procedures aimed at predicting later psychosis are prone to severe biases that compromise their prognostic validity. For example, prodromal scales such as the 16-item Prodromal Questionnaire (PQ-16; Ising *et al.*, 2012) partially rely on items from schizotypal scales such as the Perceptual Aberration Scale and the Magical Ideation Scale. We have known for many years (Peltier, 1985) that such scales have a high (negative) correlation with the tendency to respond in a socially desirable way. In addition, some PQ-16 items, such as 'I often hear unusual sounds like banging, clicking, hissing, clapping or ringing in my ears,' are ambiguous in content and may be endorsed by someone who has tinnitus (the item is presumably targeted at hallucinations, but it is not clear). Even if understood correctly, items on sensory irritations are highly problematic as 50–75% of patients with depression (Moritz *et al.*, 2014*b*) and obsessive-compulsive disorder (Moritz *et al.*, 2014*a*, 2018; Röhlinger *et al.*, 2015), who usually do not develop schizophrenia, 'hear' or 'see' their intrusive thoughts from time to time or display other psychotic-like experiences (Kelleher *et al.*, 2012; Hodgekins *et al.*, 2018).

Schizotypal as well as prodromal scales often tap visual hallucinations (e.g. 'I have seen things that other people apparently can't see' from the PQ-16). The same applies to body symptoms [e.g. 'I sometimes have had the feeling that my body is abnormal' (Perceptual Aberration Scale) or 'I feel that parts of my body have changed in some way, or that parts of my body are working differently than before' (PQ-16)], although these are common in other disorders too and are regarded as less specific than auditory phenomena in the schizophrenia spectrum (Dudley *et al.*, 2019). These items aim to capture bodily delusions but may be responded to positively by individuals who complain about 'pins and needles' and neurological symptoms such as polyneuropathy. Endorsement of schizotypal and other psychotic-like experiences are not specific to schizophrenia; patients with psychiatric disorders other than schizophrenia sometimes achieve elevated values or even similar scores on such scales as people with schizophrenia (Scherbarth-Roschmann and Hautzinger, 1991; Moritz *et al.*, 2019). Similarly, psychotic-like experiences, as measured with the Peters Delusions Inventory, are common in individuals with depression and anxiety (Varghese *et al.*, 2011).

Cut-offs need to be adjusted for culture, country, age, and also education level. Students often display scores as high as those of patients with schizophrenia on scales tapping schizotypy/psychosis-like experiences (Schutte and Malouff, 1995). With respect to language and culture, it has been shown that scores on the Schizotypal Personality Questionnaire (SPQ) are higher in the U.S. population (Raine, 1991) than in Britain or Germany (Klein *et al.*, 1997) and that individuals in all of these countries, in turn, score much higher than individuals in China (Chen *et al.*, 1997), Italy (Daneluzzo *et al.*, 1998), and the Caribbean (Barron *et al.*, 2015). Such cultural differences clearly raise questions about the usefulness of global algorithms (Chung *et al.*, 2013).

Most assessment procedures do not readily take into account the compelling evidence that depression and aggravation/overreporting (e.g. in the hope of faster and more intensive treatment) may lead to a considerable inflation of false-positive allocations. This is not a new finding (Schutte and Malouff, 1995).

We regard it as a great step forward that assessments in this area are increasingly incorporating interviews. The aforementioned problems do, however, also apply to interview scales such as the Comprehensive Assessment of At Risk Mental State (CAARMS; Yung *et al.*, 2005), albeit perhaps to a lesser extent. However, a recent meta-analysis (Oliver *et al.*, 2018) concludes

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that the prognostic accuracy of the CAARMS is acceptable but much lower than previously reported and that its specificity is poor.

We also appreciate that the advocates of the basic symptom concept of Huber and Süllwold (Gross and Huber, 1985; Süllwold, 1991) recommend that cognitive basic symptoms, the most predictive basic symptoms for subsequent schizophrenia, should be assessed with expert ratings in view of the diagnostic problems faced by self-report scales such as the Frankfurt Complaint Questionnaire (for a discussion see Schultze-Lutter *et al*., 2007). And, indeed, expert rating scales for basic symptoms seem to have some predictive value (Schmidt *et al*., 2015). Still, this cannot circumvent the problem that the assessment of cognitive deficits such as the inability to divide attention, which is an item from the Schizophrenia Proneness Inventory for Adults (Schultze-Lutter *et al*., 2007), is not verified with objective tests but relies on what the individual discloses, and there is clear evidence that subjective cognitive complaints are poorly related to objective neurocognition but highly correlated with depression (Moritz *et al*., 2004). Moreover, metacognitive problems are common in patients with schizophrenia as well as in those at risk, which also compromises the validity of such self-assessments (Moritz *et al*., 2016). In a recent study (Moritz *et al*., 2019), we found a medium correlation between the endorsement of schizotypal symptoms and items from an infrequency scale (i.e. endorsement/presence of essentially impossible phenomena such as writing with both hands equally well and equally fast), challenging the validity of symptom self-reports. Other biases may reflect the phenomenon that some patients do not disclose psychotic symptoms until after the interviewer has gained their trust. This can lead to the observation of a paradoxical worsening over time in patients who in fact have improved; more insight and less suspiciousness might enable them to acknowledge symptoms they were afraid to disclose earlier, did not recall during the initial interview, or did not deem pathological at baseline, resulting in pseudo-deterioration over time.

Lack of conclusive evidence that early intervention prevents transition to psychosis

A Cochrane meta-analysis indicates that we cannot reliably prevent transition to psychosis (Marshall and Rathbone, 2011), neither with psychotherapy nor with antipsychotic medication that – even when atypical antipsychotics are prescribed – may cause long-term (and partially irreversible) damage such as tardive dyskinesia or metabolic syndrome. This conflicts with more favorable meta-analyses (van der Gaag *et al*., 2013; Schmidt *et al*., 2015) suggesting that specialized treatment led to a transition risk reduction by 54% at 12 months and 37% at 24- to 48-month follow-ups [for a critical evaluation see Amos (2014) and Preti *et al*. (2014)]. A more recent network analysis failed to find any advantages of specialized treatments over need-based treatment for prodromal patients (Davies *et al*., 2018), while another recent analysis suggests that there is a 'slight trend' that cognitive-behavioral therapy can reduce attenuated positive symptoms at long-term follow-up (Devoe *et al*., 2019). Research in this area should continue; perhaps one day treatment will be found that can reliably delay or prevent later psychosis for the vast majority of individuals. However, for the time being, it seems to us that treatment confined to the individual's current problems (i.e. need-based intervention) is sufficient (Conrad *et al*., 2017; Albert *et al*., 2018), in which case diagnostic labels should be avoided. This also applies to the use of antipsychotic medication, which, according to European guidelines for treatment of such patients (Schmidt *et al*., 2015), should only be given in exceptional circumstances for acute symptoms and not for those that are only anticipated.

Early detection centers should be renamed and their treatment targets reconsidered

We would like to offer some recommendations. Individuals suffering from psychological problems should be offered need-based treatment. Although some of their impairments, symptoms, or biases may indeed precede later psychosis, a large subgroup will remain *happy* (McCreery, 1993) or *benign schizotypes* (Jackson, 1997), and either the abnormalities will subside on their own (*developmental transitional syndrome* in adolescence) or will develop other nonpsychotic disorders (van Os *et al*., 2009; Armando *et al*., 2010; Kelleher *et al*., 2014; Lin *et al*., 2015; Nam *et al*., 2016; Hodgekins *et al*., 2018; Beck *et al*., 2019). At the same time, therapists must do everything possible to reduce the impression that the possibility of psychosis is looming over the individual. Contemplating the diagnosis of psychosis may prompt many clinicians to prescribe antipsychotics (Yung, 2010), whose adverse effects on the young brain are unknown (Liu and Demjaha, 2013). While current predictors explain some variance, the present data do not permit definite conclusions about individual cases; in addition, we still have no treatment that can justify hope in so-called prodromal individuals. As discussed, the sword of Damocles of the possibility of later psychosis is frightening for many, and this can lead to secondary symptoms that trigger or (ironically) perhaps even cause what early detection centers seek to avert. Anticipatory suicides need to be prevented (e.g. the suicide of a person with certain schizotypal symptoms who has seen the suffering of a biological relative with the full-blown disorder). Therefore, therapists should target the immediate problems causing distress in their patients, which even in the manifest cases tend to be depression and low self-esteem rather than the core positive symptoms (Moritz *et al*., 2017).

Steps in this direction have already been made. A good example of this new trend are facilities such as headspace (Australia) and soulspace (Germany), which are facilities for young individuals in crisis, including those with at-risk symptoms (Bassilios *et al*., 2017; McGorry *et al*., 2019). To avoid stigma, these facilities are separate from institutions for individuals with *established* psychiatric disorders. While monitoring the individuals for signs of more severe stages of psychopathology, the connection between certain symptoms with subsequent schizophrenia is de-emphasized. Instead of promulgating a categorical view of mental illness, which induces the fear of eventually falling into this undesired category, a continuum view of mental health and mental illness offers a better framework for preventive services and thus avoids stigmatization (Schomerus *et al*., 2016) but still offers help for manifest problems. Such services should offer staged care ranging from low-threshold self-help and online intervention for less severe cases and face-to-face intervention, which may also include pharmacotherapy, for those with more distressing symptoms. These facilities should use hope-oriented and stigma-free labels; in view of the multitude of outcomes of adolescent (attenuated) positive symptoms, cataclysmic terms such as *early detection*, *prodrome/al* and *risk* should be avoided. At this time, such developments are in their infancy, and many prodromal clinics treat

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individuals at alleged risk of psychosis as if they are patients with an established psychiatric diagnosis.

To conclude, we should not catastrophize an individual's future that can be neither reliably predicted nor ameliorated.

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