"At risk mental state" clinics for psychosis - An Idea Whose Time Has Come - and Gone!

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Introduction

The idea of early intervention (EI) services for people suffering their first episode of psychosis (FEP) was conceived as a way to improve the long-term outcomes of the illness (Falloon, 1992; Falloon *et al*., 1996). Indeed, the results of EI services, such as the Lambeth Early Onset (LEO) (Craig *et al*., 2004) and OPUS (Hastrup *et al.*, 2013), have been encouraging and led to such services becoming widely established. In a further extension of the idea, specific clinical criteria were proposed to identify people who were at high clinical risk of developing psychosis in the subsequent 1-2 years (Yung *et al*., 1996; Yung *et al.*, 2006). The definition of this pre-psychosis phase in which people manifested the At Risk Mental State (ARMS) (Fusar-Poli *et al*., 2013) was followed by claims that identification of such individuals who were at ultra-high risk (UHR) of developing psychosis, provides a valuable opportunity to prevent a substantial proportion of pre-psychotic individuals from transitioning to clinical psychosis (Yung *et al*., 2005). Subsequently, detection of young people with the ARMS has become a popular prevention strategy (Reddy, 2014) with the creation of ARMS clinics in many countries (Addington *et al*., 2008; Cannon *et al*., 2016; Fusar-Poli *et al*., 2013; Yung *et al*., 2006).

ARMS clinics are specialised mental health services for help-seeking people, who are usually aged 14-35 years old and considered to be at UHR of developing psychosis. The stated purpose of these clinics is to reduce, or deter, transitions from the ARMS state to clinical psychosis (Fusar-Poli *et al*., 2013; Green *et al*., 2011). Many studies of ARMS clinics report evidence for their benefits and provide “evidence-based recommendations” or “guidance” for the treatment of such individuals (Killackey and Yung, 2007). However, the strength of such claims has not been established (Morrison *et al*., 2012). The purposes of this article are two-fold. First, we sought to review the robustness of the claims that ARMS clinics have the capacity to prevent transition to psychosis; and second, we aimed to raise the question of whether it may be more beneficial for prevention of psychosis to adopt a public health approach, which in turn would target risk factors for the illness onset rather than focusing on the ARMS phase.

Defining the At Risk Mental State (ARMS) phase

The ARMS phase is characterised by either 'attenuated' psychotic symptoms, or full-blown psychotic symptoms that are brief and self-limiting (Fusar-Poli *et al*., 2013). It may also manifest as a significant decrease in functioning in the context of a familial (presumed genetic) risk for schizophrenia, or subtle subjective disturbances of cognitive processes, thinking, perception, moods and behaviours (Yung *et al*., 2003; Yung *et al*., 2006). To increase objectivity and diagnostic accuracy of this construct, several scales, such as the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung *et al*., 2005) and the Structured Interview for Prodromal Syndromes/Scale of Prodromal Symptoms (SIPS/SOPS) (Miller *et al*., 2003; Woods *et al*., 2009) have been designed to measure these symptoms with arguably reasonable inter-rater reliability (Loewy *et al*., 2011).

However, it has been reported that as many as 84% of those individuals who were identified as being at risk for the illness using these scales did not develop a psychotic disorder within 2-3 years (i.e., these individuals are normally referred to as "false positives") (Corcoran *et al*., 2010). Even when the diagnosis of the ARMS was made by experienced clinicians, the false-positive rate remained substantially high (47%) (Yung *et al*., 2008). This may suggest that the difficulty in identifying individuals with the ARMS lies in defining the construct. Indeed, it has been shown that the proportion of adolescents who meet criteria for the ARMS varies from 0.9% to 22.6% depending on slight variations in the ARMS criteria (Kelleher *et al*., 2012). Furthermore, attempts to identify specific biological markers of the ARMS phase and predictors of a transition from the ARMS to clinical psychosis have been unsuccessful (Castle, 2012; Wood *et al*., 2013). It has therefore been argued that early intervention on the basis of the screening criteria for subclinical psychosis is not feasible in the general population (van Os, 2005).

Services for the ARMS phase create useful pathways to care – but for whom?

Most clinics for young people who meet criteria for the ARMS, accept referrals via a wide range of means including mental and non-mental health professionals, and non-health organisations (Fusar-Poli *et al*., 2013; Green *et al*., 2011). These teams attempt to respond to all referrals and conduct the first assessment within the first week of the referral being made. This is considerably shorter than most psychiatric services can offer. For those patients who are judged to meet criteria for the ARMS, the services provide a 2-3 year treatment plan (Green *et al*., 2011).

However, there is a question of whether individuals who contact the ARMS services and meet criteria for the ARMS are representative of all pre-psychotic individuals. For example, Ajnakina *et al*. (2017) showed that those with the ARMS, who attended an ARMS clinic in South-London and later developed clinical psychosis, were more likely than those FEP patients who had not attended such a clinic, to be born in the UK and have strong family support, with migrants being less likely to access the services. Others showed that the young people who met criteria for the ARMS and attended an ARMS clinic were likely to be employed and have higher educational achievements (Addington *et al*., 2012; Valmaggia *et al*., 2015).

The reason for such differences is likely to be that the ARMS services require individuals to be help-seeking. Migrants and ethnic minorities are well-known to be less trusting of mental health services than those from the host population (Morgan *et al*., 2006). Availability of supportive families and strong social networks, which are frequently absent in those with clinical psychotic illness (Sundermann *et al*., 2014), are also important factors for help-seeking (Morgan *et al*., 2006). Moreover, to recognise “not-quite-psychotic” symptoms, the potential patients, or their relatives, need to have some knowledge of such symptoms plus insight into their potential illness significance. It is not surprising, therefore, that those patients who have been accepted under the care of the ARMS services have better insight compared to psychosis patients who do not reach these services (Lappin *et al*., 2007). Another reason why

prodromal samples cannot be representative of all pre-psychotic individuals is that some patients present so acutely (Ajnakina *et al*., 2017) that even if they were willing to accept help there is no time to intervene (Shah *et al*., 2017). Therefore, the evidence suggests that under current pathway configurations, services for those who meet the criteria for the ARMS appear to attract a subgroup of pre-psychotic individuals who are atypical of all those people who will develop FEP. This in turn should raise some doubts as to whether some of the benefits claimed for ARMS clinics (Valmaggia *et al*., 2015) are actually a reflection of the population attracted to the ARMS clinics, rather than the care offered by the clinics. The nature of the unselected, representative and non-help seeking population samples remains unknown.

Have the transition rates fallen?

Early studies reported that 30-54% of those with the ARMS went on to develop full psychotic disorder in the following 12-24 months (Fusar-Poli *et al*., 2012; Miller *et al*., 2002; Yung *et al*., 2003). Some more recent reports, however, have suggested that the transition rates from the ARMS phase to clinical psychosis are as low as 8-17% within a 2-year period (Morrison *et al*., 2012; Carrion *et al*., 2016; Conrad *et al*., 2017; Malla *et al*., 2017). It is possible that the reduced reported transition rates may be an outcome of successful interventions implemented by ARMS clinics (McGorry *et al*., 2006; Nelson *et al*., 2016).

However, it is likely that the reduced estimated transition rates are, at least in part, a consequence of other factors such as changes in characteristics of the sample or their pathways to care (Wiltink *et al*., 2015) as well as different definitions of what constitutes transition to psychosis employed across studies (van Os and Guloksuz, 2017). Further, van Os (2005) highlighted that the high positive predictive values presented by some studies when predicting the transition from the ARMS phase to clinical psychosis (Miller *et al*., 2002; Yung *et al*., 2003) are actually an outcome of the sample enrichment that results from the mainstream sample selection procedures. This in turn leads to spuriously increased incidence

and predictive values (van Os, 2005). In fact, when the transition rate was estimated based on the actual prevalence of the ARMS in the general population it was shown to be around 1% (van Os, 2005).

Another important reason why transition rates are lower than previously reported may be that the identified pre-psychotic patients are diluted in more recent studies by large numbers of patients with other psychiatric problems. This may be due to referrers realising that the clinics provide an opportunity for a rapid clinical assessment of distressed young people. A recent review suggested that over 80% of individuals referred as “at risk for psychosis” will never develop clinical psychosis (van Os and Reininghaus, 2016). This raises ethical issues relating to medication exposure and stigma among those who were false-positives (Bentall and Morrison, 2002; McGlashan, 2001). Even for those individuals who were identified at UHR by the ARMS services, the evidence for effectiveness of the interventions that these prodromal clinics offer is weak (Castle, 2012).

Criticisms of the ARMS Concept

The assumption behind AMRS clinics is that the ARMS state is what van Os and Murray RM (2013) called a “schizophrenia light”: defined according to an (arbitrary) cut-off of psychosis severity or a (similarly arbitrary) diagnostic concept of “schizophrenia spectrum”. People can cross and re-cross this boundary several times (van Os and Murray, 2013). As the expression of psychosis naturally fluctuates in intensity and severity within individuals over time, temporary amelioration of psychosis at the time of the baseline assessment may cause these people to be wrongly assigned to the UHR group rather than the psychotic group.

Furthermore, psychotic symptoms are much more common than previously realised. Indeed, they are found in about 5% of the general population, 9% of adolescents, and 25% of people with (non-psychotic) common mental disorders (Linscott and Van Os, 2013; van Os and Reininghaus, 2016; Zammit *et al*., 2013). Interestingly, one study found that 16% of non-

psychotic young people who were assessed and found not to meet the UHR criteria made a transition to clinical psychosis (Carr, 2012). These figures vary depending on different methods of data acquisition and categorisation (David, 2010). Thus, it is difficult to define with certainty when an individual transits from pre-psychotic symptoms to the ARMS, and at the other end from the ARMS to clinical psychosis (David and Ajnakina, 2016).

To further complicate matters, the symptoms that are at the core of the definition of the ARMS phase are frequently present in other mental disorders (Kelleher *et al*., 2012; van Os and Guloksuz, 2017). Studies of UHR groups show that they consist largely of people with common mental disorders such as anxiety and depression (Addington *et al*., 2017; Fusar-Poli *et al*., 2014). Therefore, the presence of psychotic symptoms in themselves should not be seen as an indication of the risk to making the transition to psychosis (Murray and Jones, 2012).

ARMS clinics are morphing into clinics for youth mental health

The realisation that the most common diagnoses reported in young people attending the ARMS clinics are anxiety, depression and personality disorders (Kelleher *et al*., 2012) prompted McGorry, one of the founders of the ARMS movement, to broaden the scope of such clinics from focussing on those at risk for psychosis to becoming more general outreach clinics for youth who are at risk for any mental disorders (Malla *et al*., 2016; McGorry *et al*., 2013). Thus, the idea of specific clinics for pre-psychotic individuals has been replaced with cross-diagnostic youth mental health facilities with much broader and more inclusive (and laudable) purpose of identifying and caring for young people with mental health problems (Malla *et al*., 2016; McGorry *et al*., 2013). The inclusive concept of youth mental health is broad enough to encompass any potential abnormality and does not require being either severe or specific enough to warrant a clinical diagnosis. This approach has much to commend it but an early evaluation of such services in Australia foundthat evidence of benefit was inconclusive (Hilferty *et al*., 2015).

A Public Health Approach

Can prodromal clinics ever prevent development of clinical psychosis in a significant number of pre-psychotic individuals? Ajnakina *et al*. (2017) carried out a comprehensive evaluation of FEP patients in an area of South-London which has had a well-developed ARMS service for more than ten years serving the same catchment area. They found that only 4.1% of FEP patients had previously made contact with ARMS services and met the ARMS criteria (most presented to FEP psychosis directly or via other routes). This very low proportion suggests that the scope for ARMS services reducing or postponing the onset of psychosis is limited as is their public health or economic impact (van Os and Guloksuz, 2017).

We recognise, of course, that ARMS clinics have provided a valuable source of pre-psychotic patients for research. This in turn has ignited an explosion of research findings (Anticevic *et al*., 2015; Cannon *et al*., 2015; Walker *et al*., 2013). For example, it has been shown that individuals with the ARMS who proceed to develop clinical psychosis have an excess capacity to synthesise striatal dopamine (DA) which increases further as they get nearer to clinical psychosis, compared to healthy controls (Howes *et al*., 2011) and that cortical volume loss may be accelerated in the months prior to transition (Cannon *et al.,* 2015). Nonetheless, this does imply that the process of developing psychosis has already begun in people with the ARMS. Therefore, it reinforces the point that intervening at this stage may already be too late.

The development of ARMS clinics has also increased awareness of a greater opportunity for prevention and early intervention. In medicine, preventive approaches to illnesses such as heart disease, bronchitis, or obesity do not focus on identifying individuals just on the brink of developing the disorder or carrying biological markers for it. Instead, they target the known risk factors for the conditions, and encourage members of the general public to change their behaviour, for example start exercising or reduce calorie or cigarette intake, with the aim of reducing their risk of developing the condition.

A similar approach should be adopted for psychosis. Indeed, a number of risk factors for developing psychosis have been identified and replicated. These include obstetric events, childhood adversity, urban birth and upbringing, and adverse life events (Gaag *et al*., 2016; Radua *et al.,* 2018; Stilo and Murray, 2010). Moreover, a recent large and methodological rigorous study has provided further empirical evidence for the link between risk for psychosis onset and immigration (Jongsma *et al*., 2018).

The evidence that cannabis use is an important risk factor for later developing psychotic symptoms and/or psychotic disorder is especially strong (Murray *et al*., 2016). This risk has been shown to increase linearly with a greater frequency, longer length of use, and the stronger potency of the cannabis used (Di Forti *et al*., 2014; Marconi *et al*., 2016). Importantly, it has been demonstrated that a substantial proportion of first episode psychosis cases (24% in London) would have been prevented if no one consumed cannabis of high potency (Di Forti *et al*., 2015). The risk increasing effects of cannabis extend to individuals who meet criteria for ARMS, reiterating the importance of this risk factor for preventative purposes. Indeed, it has been reported that individuals meeting criteria for ARMS not only have high rates of cannabis use (Carney *et al*., 2017) but also that those who have used cannabis at least weekly have significantly more severe positive psychotic symptoms than non-cannabis users (Nieman *et al*., 2016).

In the long-term, attempts to reduce exposure to these risk factors for psychosis should be made. Though this will not be easy since the pathogenic mechanism underlying the link between some of these risk factors and psychosis is not yet understood; for example, it is likely that urban living is a proxy for one or more more specific psychotogenic factor(s). Furthermore, it may be very difficult to diminish exposure to some risk factors, such as child abuse or migration. However, an obvious place to start is by attempting to reduce society's consumption of high-potency cannabis through public education (Gage *et al*., 2016; Di Forti *et al*., 2015). Unfortunately, the legalisation of cannabis for "medicinal" or "recreational" use across states of the USA has been accompanied by an increase in the use and potency of

cannabis (Rehm and Fischer, 2015; Heslin et al, 2018). Thus, public policy in North America appears to be moving in the opposite direction. Psychiatrists need to be more vocal in drawing attention to the risks to mental health involved in policies which increase consumption of high potency cannabis.

Conclusion

The idea of identifying individuals before they become unwell is a worthy idea, especially in the era when our treatments for psychosis are far from perfect. However, it is clear that the task of making a major contribution to the prevention of psychosis is beyond the power of the ARMS clinics. A public health approach to prevention of psychosis has the potential to be more effective. Nonetheless, should such the ARMS clinic continue to exist, they face an important challenge in regard to developing pathways which will attract a broader and more representative group of individuals to access their services.

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Conflict of interest

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