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CBT in the prevention of psychosis and other severe mental disorders in patients with an at risk mental state: A review and proposed next steps

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ABSTRACT

Patients with an 'At risk mental state' (ARMS) for developing psychosis can be treated successfully with CBT to postpone and prevent the transition to a first psychotic episode. A characteristic of individuals that meet ARMS criteria is that they are still open for multiple explanations for extraordinary experiences. CBT aims to normalize extraordinary experiences with education and to prevent delusional explanations. The treatment is not only effective, but also cost-saving in averting psychosis as well as in reducing disability adjusted life years at 18- and 48-month follow-up. Profiling within the ARMS group results in a personalized treatment. The screening and early treatment for ARMS fulfills all the criteria of the World Health Organization and is ready to be routine screening and treatment in mental health care.

At the same time, ARMS patients are complex patients with multi-morbid disorders. Especially childhood trauma is associated to ARMS status, together with co-morbid PTSD, depression, substance abuse and anxiety disorders. Psychotic symptoms appear to be severity markers in other non-psychotic disorders. Preventing psychosis in ARMS patients should be broadened to also address other disorders and aim to reduce chronicity of psychopathology and improve social functioning in general.

Several mechanisms play a part in psychopathology in ARMS patients such as stress sensitivity as a result of adverse experiences, dopamine sensitivity that is associated with salience and aggravates several cognitive biases, dissociation mediating between trauma and hallucinations, and low self-esteem and self-stigma. New avenues to treat the complexity of ARMS patients will be proposed.

1. Introduction

Schizophrenia still has a poor prognosis despite the innovations in pharmaceutical and psychosocial treatment. The duration of untreated psychosis (DUP) was found to be associated with poor outcome and suggested as a modifiable risk factor (McGlashan, 1999). A recent meta-analysis with many studies found that a long DUP was robustly associated with poor outcome (Penttilä et al., 2014). Birchwood and colleagues introduced the concept of the critical period of five years in which patients with a short DUP needed optimal treatment to substantially improve the outcome (Birchwood et al., 1998). This has led to the implementation of numerous early intervention services. In these services, some patients were detected with attenuated psychotic symptoms, who did not fulfill the criteria of a psychotic disorder (Yung and McGorry, 1996). The profile was named 'At Risk Mental State' (ARMS) (Yung et al., 2005). Ultra-high risk (UHR) is another name for the same profile (Phillips et al., 2000). The ARMS population showed high rates of transition into psychosis and this made the ARMS profile a new target for indicated prevention of psychosis and the prevention of accompanying intensive treatment trajectories (Yung et al., 2004).

1.1. Risk profile

The assessment instrument of ARMS was developed by an Australian group and set arbitrary, but reliable, criteria for 1) psychosis, 2) ARMS, or 3) neither (Yung et al., 2005). The ARMS-profile comprises three subgroups:

1) a group with attenuated psychotic symptoms;
2) a small familial risk group with a first degree relative with a psychotic disorder; and.
3) a small group with a brief limited intermittent psychotic symptoms (BLIPS) who had a florid psychosis that lasted less than seven days and remitted spontaneously without treatment.

All subgroups are also characterized by social decline in recent months (Yung et al., 2006). Individuals so identified merit clinical care for current symptoms and impaired function. The transition risks at

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48 months differ between the subgroups varying from 38% in the BLIPS group, 24% in the attenuated symptoms group and 8% in the familial risk group (Fusar-Poli et al., 2016a).

There are many routes to psychosis. This equifinality suggests that various etiological mechanisms and developmental pathways have a complex interplay. ARMS patients are found in all DSM classifications in help-seeking patients and especially in mood and anxiety disorder, substance abuse, and personality disorder (Rietdijk et al., 2012). Trauma experience is very common in ARMS with 86.8% (Kraan et al., 2015b) and associated with multi-morbidity in ARMS patients (Kraan et al., 2015a, 2017; van Dam et al., 2015). Exposure to traumatic life experiences can significantly impact the pathogenesis of psychotic experiences as either a precipitating or exacerbating factor, and can lead to psychosis outcomes through myriad pathways that intersect with genetic or other environmental risk factors (Gibson et al., 2016). ARMS is thus a heterogeneous risk profile and not a disorder.

1.2. Why treating a risk profile?

Treating heterogeneous risk profiles can be beneficial. The treatment of blood pressure and cholesterol among other preventive interventions has reduced coronary disease with 50% in the Netherlands (Koopman et al., 2016). The progress in outcome of cancer treatment is also due to early detection and early treatment, when prognosis is still good. Can this staging model be applied to psychosis as well?

The difference between ARMS and FEP can be more than fluctuation on a continuum. While ARMS patients seek help for depression or anxiety, they all fear that the perceptual aberrations signal imminent mental breakdown. Psychotic patients do not in general seek help for their psychosis as they consider the experiences not as symptoms, but as a reality. That is a second difference, psychotic patients by definition have lost part of the awareness and insight that something is wrong, while ARMS patients are painfully aware that they are losing control over their mental apparatus. They still have several explanations for their experiences and convictions can change rapidly during the day, while psychotic patients have delusional certainty and feel annoyed by different views of others. This difference in uncertainty versus certainty also explains why ARMS patients are more receptive to psychoeducation and eager for therapy, while psychotic patients are generally less interested in psychoeducation as they consider themselves to be healthy and not ill. The psychotic patient acts on his delusions, while the ARMS patient often does not. Although psychotic experiences can largely be considered as continuous experiences, these differences in phenomenology support the idea of meaningfully different stages. This also becomes evident in the differences in prognosis and the course of the symptoms. The prognosis declines with progression through the stages of psychosis (see Table 1).

The risk for relapse or recurrence is a lifetime risk in psychotic disorder, while the risk of transition to psychosis is time limited in ARMS with no more transitions after 10 or more years follow-up (Nelson et al., 2013). Postponing transition for 10 years may mean lifetime prevention.

1.3. Why CBT for ARMS?

A number of studies were conducted to prevent the transition to psychosis in patients with the ARMS profile. The interventions were antipsychotic medication, CBT, polyunsaturated fatty acids (PUFAs), or integrated therapy including psychoeducation, assertive community treatment and social skills training (Nordentoft et al., 2006) or individual cognitive-behavioral therapy, group skills training, cognitive remediation and multifamily psychoeducation (Bechdolf et al., 2012). Meta-analyses showed that CBT was effective in reducing transition to psychosis (Hutton and Taylor, 2014; van der Gaag et al., 2013b). Antipsychotic medication showed efficacy, but no more than CBT. Side-effects of medication resulted in low tolerance. PUFAs were promising, but a recent large study showed no effect at all (McGorry et al., 2016). Integrated psychosocial interventions appear promising, but need replication with more methodologically rigorous studies. Considering this evidence base, the European guidelines based on meta-analyses recommend the detection of ARMS subjects with screening and structured diagnostic interviews and recommend CBT as a first line treatment to prevent transition to psychosis (Schmidt et al., 2015; Schultze-Lutter et al., 2015).

2. Cognitive model of ARMS and the methods and structure of the CBT intervention

The neurocognitive model of psychosis has been refined in the last decade, but still rests on aberrant salience, and biased appraisal processes (Broyd et al., 2017; Kapur, 2003; van der Gaag, 2006).

The bottom-up biological process consists of increased striatal dopamine release. This is associated to aberrant salience. Aberrant salience opens the gates to consciousness for trivial stimuli to enter the center of attention and the salient stimulus cries out for an appraisal. The salient subject feels that the stimulus has personal importance and that acting upon it is needed (Kapur, 2003). Aberrant salience in ARMS patients can progress to psychotic symptoms (Howes et al., 2017).

The appraisal process that is elicited by aberrant salience is a key mechanism of developing delusions. Emotional appraisal characterized the group that evolved from developing a psychotic symptom to a clinical condition in need of care (Hanssen et al., 2005). Those patients with hallucinatory experiences at baseline who developed psychotic disorder at 3-years follow-up, had developed delusional experiences at 1-year follow-up. Other authors concluded that clinical outcome is related to the development of secondary delusional beliefs (Daalman et al., 2012; Krabbendam et al., 2004).

CBT should target appraisal processes that accompany perceptual aberrations and suspiciousness to normalize the extraordinary experiences and to prevent delusion formation and avoidance behaviors that consolidate symptoms.

The appraisal processes in ARMS patients are biased by several cognitive biases: jumping to conclusions, selective attention to threat and an externalizing and personalizing bias. Jumping to conclusions (JTC) is characteristic for delusional patients and for ARMS patients

Table 1
Outcome characteristics of the different stages in psychosis.

Stage	Remission	Persistence	Psychotic episode	Reference
1a PLE	84%	8%	8%	(Hanssen et al., 2005)
1b ARMS help-seeking	46%	27%	27%	(Simon et al., 2013)
1b EDIE-NL control	57%	19%	24%	(van der Gaag et al., 2012)
1b EDIE-NL experimental	71%	17%	12%	(van der Gaag et al., 2012)
		Multiple episodes	Permanent psychosis	
2 FEP	16% (≥3-yr F-U)	84%		(Fusar-Poli et al., 2016a)
3abc – 4 recurrent psychosis	14%	76%	10%	(Jääskeläinen et al., 2013) (Wiersma et al., 1996)

PLE = psychotic-like experiences in the population; ARMS = help-seeking ultrahigh risk; FEP = first episode psychosis; 1a–4 are stages in psychosis history.

(Broome et al., 2007; Winton-Brown et al., 2015). Aberrant salience and enhanced threat anticipation are associated with an increased intensity of psychotic experiences in ARMS and psychosis (Reininghaus et al., 2016). Psychotic patients with both persecutory and grandiose beliefs showed an externalizing style for negative events, while those with persecutory beliefs in combination with depression showed a relatively externalizing style for positive events (Jolley et al., 2006). ARMS participants showed a greater tendency to perceive hostility and to blame others in negative, ambiguous situations, and these attribution style biases were linked to the level of paranoia and persecution beliefs (An et al., 2010). Another study however did not confirm these findings (Devylder et al., 2013).

CBT can address JTC by stressing the need for weighing alternative explanations of situations by for instance using pie charts. Attention to threat can be explored by exercises into selective attention in which patients learn that selective attention results in increased observations of a certain stimulus and also increases anxiety. The externalizing and personalizing can for instance be tested with behavioral experiments.

Furthermore, patients are encouraged to discuss their extraordinary experiences and their interpretations of the experiences with their friends and relatives. The assumption is that reality always is a shared reality. The therapist encourages to stay socially active, to keep going to school and/or work, and to test negative appraisals in behavioral experiments (van der Gaag et al., 2013a).

2.1. Frequent comorbidities

Most ARMS patients are also depressed, have low self-esteem and have negative schemata about self, others and the world. Precipitating factors are childhood trauma, bullying, social withdrawal and isolation. CBT for ARMS may sometimes integrate the treatment of PTSD and depression.

Cannabis use is discouraged. In general, this takes remarkable little effort, because most ARMS patients have noticed that paranoid ideation and other subclinical psychotic symptoms are amplified by cannabis use and education that cannabis is a risk factor for a first episode of psychosis helps to stop using cannabis in many patients.

3. Results of the different trials

Several RCTs have been conducted. The first one was the EDIE trial by Morrison with 60 patients (Morrison et al., 2004). French and Morrison wrote a book with the protocol (French and Morrison, 2004). The CBT intervention is based on a formulation-driven cognitive model that prioritizes a collaboratively agreed problem list. It is problem-oriented, time-limited and educational treatment, using collaborative empiricism with guided discovery, behavioral experiments and homework tasks. The model draws on strategies for change, including normalization, generating and evaluating alternative beliefs, safety behaviors, metacognitions, core beliefs, social isolation and relapse prevention. Strategies used were selected in accordance with the formulation and key problems identified on the participant's problem list.

Most other RCTs used the French and Morrison approach (Addington et al., 2011; Morrison et al., 2012; Stain et al., 2016; van der Gaag et al., 2012).

The Australian study in Newcastle enriched the French and Morrison with Motivational Interviewing-CBT skills for those who presented with hazardous substance misuse (Stain et al., 2016).

The Dutch EDIE-NL enriched the protocol with psychoeducation on dopamine sensitization and the effects on perception and reasoning and exercises to experience cognitive biases to be aware of them and correct for the biases (van der Gaag et al., 2013a).

The Australian trial from Melbourne used their own four modules: 1) stress management, 2) depression/negative symptoms, 3) coping strategies for positive symptoms, 4) other comorbidity such as anxiety disorder, PTSD, substance use (McGorry et al., 2013; Yung et al., 2011). The latter treatment is an educational and not a personalized formulation-driven approach.

An important difference between these trials is whether the social functioning criterion was included in the prognostic model. Studies that included attenuated symptoms without decreased social functioning had much lower transition rates.

Four meta-analyses were published. The Stafford et al. meta-analysis evaluated five RCTs at 6–12 month outcome and found a reduced number of transitions to psychosis and a Risk Ratio (RR) of 0.54 (Stafford et al., 2013). The van der Gaag et al. meta-analysis used the same five RCTs but had access to the 12 month outcomes of the Melbourne study and found a RR of 0.52 (van der Gaag et al., 2013b). The total number of patients of the five studies was 708 subjects.

The Hutton et al. meta-analysis included the German study of CBT in a comprehensive psychosocial package (Bechdolf et al., 2012) and also found a RR of 0.52 (Hutton and Taylor, 2014). The Schmidt et al. meta-analyses decided to take in ten studies (also medication and family intervention) as they were homogeneous in their effects and found a 12-month RR of 0.44 (Schmidt et al., 2015).

The Newcastle study had 57 participants, but came out after the meta-analyses and was negative in very young ARMS patients (Stain et al., 2016). Including the study with the five CBT trials resulted in a preserved RR of 0.54.

Another important result is on screening versus referral. The EDIE-NL project screened all help-seeking patients in mental health services in catchment area of The Hague (population 650,000), while the Amsterdam catchment area (population 750,000) included referred patients without screening. Screening the general help-seeking population detected 93 ARMS patients, while referral detected 40 patients. Especially female ARMS patients are under detected in referrals. Furthermore, the screened population had a higher transition rate than the referred group (Rietdijk et al., 2012).

Although detection and postponement and prevention are feasible, the effects on social functioning are disappointing. Preventing a psychosis does not automatically result in more friends, jobs and quality of life. Although social functioning improved at 18- and 48-months follow-up in non-converters, the improvement was not statistically significant in a meta-analysis (Schmidt et al., 2015). There must be more goals than just the prevention of transition.

4. Conclusions and future developments

CBT for ARMS is successful in postponing and preventing the transition to psychosis. The treatment effect is still significant at 48-monts follow-up and implementing screening, early detection and preventive treatment is cost saving. The patients that make a transition to psychosis do worse at follow-up and this explains the huge budget savings as preventing psychosis pre-empts future mental health costs and also reduces productivity losses (Ising et al., 2017, 2015).

4.1. Clinical implications

An important clinical implication is that waiting for referral of ARMS patients results in a low detection rate. Early intervention services should try to implement screening in help-seeking populations.

Several screeners have been developed (Kline and Schiffman, 2014). The PQ-16 is used to screen the help-seeking population in the Netherlands. The psychometric qualities of the PQ-16 were replicated in a Chinese university sample (Chen et al., 2016) as were the 29.1% of converters over a two-year follow-up (Zhang et al., 2017). The screening at the entrance of routine mental health services results in 1.4% of already psychotic people and about 4% patients who fulfill ARMS criteria (Ising et al., 2012).

Wilson and Jungner composed the ten WHO criteria that had to be fulfilled before screening may be implemented in routine care (Wilson and Jungner, 1968) and the screening and prevention of psychosis in

ARMS patients now fulfills all the criteria: 1) the ARMS profile indicates an important health problem, because 36% will develop psychosis in three years; 2) CBT is effective in reducing the transition rate; 3) a screener, diagnostic interview and treatment protocol are at hand; 4) ARMS is a latent stage of psychotic disorder; 5) the CAARMS and the SIPS are the state of the art structured interviews to diagnose the ARMS; 6) the PQ-16 is a 2-minute screen that can be applied to the general (help-seeking) population; 7) transition to psychosis results in poor prognosis and disablement; 8) there is evidence and consensus on the definition of ARMS; 9) the prevention is cost-saving; and 10) screening is already beginning to be implemented in routine mental health care in the Netherlands.

Other clinical implications are the necessity to spread preventive CBT for ARMS in mental health services. Referral will work, but routine screening of help-seeking patients in mental health services has better detection rates.

At several places in the world specialized services have been developed to screen, detect and treat patients with the ARMS profile. These high-risk services are also beneficial for patients presenting with a first episode of psychosis compared to routine mental health services. In the London OASIS team patients spent fewer days in hospital, had a shorter referral-to-diagnosis time, a lower frequency of hospital admission, and a lower likelihood of compulsory admission (Fusar-Poli et al., 2016b).

4.2. Implications for mental health services and budgets

The therapy effects in the EDIE-NL trial could be accomplished and save costs. Especially the direct medical costs were reduced and the intervention was cheaper than doing nothing at all. CBT for ARMS showed an 83% probability of being more effective and less costly than Routine Care (RC) (Ising et al., 2015). The 48-months follow-up results still showed significant effects on transition rate and also the number of patients who fully remitted from subclinical psychotic symptoms was higher in the CBT condition (Ising et al., 2016b). The societal cost-savings were even further improved with a 92% probability of being more effective and less costly at 48-months (Ising et al., 2017).

Budget Impact Analyses takes an implementation time of 6 years and then 40% of the targeted population will be included. Then the cumulative savings are calculated over the next ten years. The net cash value will be about € 26,000,000 Euro's cheaper than doing nothing in the Netherlands. The prevalence of psychotic disorders can be reduced with 15% in the long-term (Lokkerbol et al., 2016).

4.3. Further research: broadening the scope of the risk concept and the treatment targets

A major problem is that patients who do not transition still function poorly in 43% (Brandizzi et al., 2015) and have 49% depression and 35% anxiety disorder at follow-up (Lin et al., 2015). ARMS patients that have received both evidence-based treatment for their dominant axis-1 disorder and CBT for ARMS do better with 13% depression 20% anxiety disorder at 18-months follow-up (van der Gaag et al., 2012).

The field shares the critique that a single focus on transition to psychosis in ARMS is not enough (Addington and van der Gaag, 2015; Fusar-Poli et al., 2015; Lin et al., 2015). Psychotic symptoms are a severity marker in for instance depression (Wigman et al., 2014). The screening approach in all help-seeking patients in mental health services is already broadening the scope compared to projects with referred patients. The enrichment strategy with the combination of young age, help-seeking for a psychiatric classification, decline in social functioning and the 'at risk' criteria taken together selects many more people at risk for long-term treatment trajectories in mental health services (Rietdijk et al., 2012). Adding broad spectrum additional risk factors constituted a predictor model consisting of five baseline variables (observed blunted affect, subjective complaints of impaired motor function, subjectively experienced social marginalization, decline in social functioning, and distress associated with suspiciousness) may significantly improve accuracy in predicting future psychosis and persistent low functioning in a help-seeking ARMS sample of patients (Ising et al., 2016a). The profiling within the risk groups opens up personalized treatment for this group varying from short psychoeducation tot multi-specialist treatment and outreach to spouses, families, schools and workplaces to preserve social functioning.

Childhood trauma predicted poor employment outcome in ARMS patients (Cotter et al., 2017) and physical abuse and emotional neglect was negatively associated with social functioning, while childhood trauma was not associated with transition to psychosis at the 4-year follow-up in the EDIE-NL trial (Kraan et al., 2017). An effect of trauma on social functioning and not on the transition to psychosis was also found in the DUPS cohort (Kraan et al., 2015a). So, the late effects of childhood trauma contribute to persistent low social functioning, independent from attenuated psychotic symptoms. ARMS patients have been traumatized in 87% of the cases (Kraan et al., 2015b) and treating PTSD in psychotic patients is feasible, safe and effective (van den Berg et al., 2015, 2016). To improve the outcome of ARMS patients, the prevention of transition to psychosis and the treatment of PTSD are both contributing to health and social well-being and are indicated treatments.

Other psychosocial components that were suggested are social skills training and family involvement to create a supportive environment (Thompson et al., 2015).

We disagree with some critics that state that the high-risk strategy is inefficient and a public health approach is better (van Os and Guloksuz, 2017). The evidence at this moment favors the high-risk approach as in oncology and coronary diseases, while evidence for public health approaches is lacking and unlikely to accomplish. The necessary development in near future will be to combine transition psychiatry with low threshold services for young people with specialized detection of high risk patients with low incidence. Headspace, founded on the staging concept of psychotic disorders, is a good example of such a low stigmatizing access of young people to mental health services and at the same time screening for developing severe mental illness characterized by emerging psychotic symptoms.

4.4. Concluding comments

Much was accomplished in a relatively short time. Screening and treatment of subjects at high risk for developing psychosis and other major multimorbid psychiatric disorders is feasible. CBT is effective in postponing and preventing a first episode psychosis in a 4-year period. The scope of the intervention must be broadened to treatment of the multimorbid disorders in order to prevent chronicity and above all foster good social functioning. Evidence-based treatment of established disorders is important, but indicated prevention in ARMS patients can actually reduce incidence rates. There are cost savings in direct medical costs, because of reduced health care consumption, and there are also savings in society, because less people have financial benefits and more have a paid job and pay taxes. CBT for ARMS has been included in the European guidelines and awaits dissemination and implementation in mental health services.

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Conflict of interest

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