Improving outcomes of first-episode psychosis: an overview

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Outcomes of psychotic disorders are associated with high personal, familiar, societal and clinical burden. There is thus an urgent clinical and societal need for improving those outcomes. Recent advances in research knowledge have opened new opportunities for ameliorating outcomes of psychosis during its early clinical stages. This paper critically reviews these opportunities, summarizing the state-of-the-art knowledge and focusing on recent discoveries and future avenues for first episode research and clinical interventions. Candidate targets for primary universal prevention of psychosis at the population level are discussed. Potentials offered by primary selective prevention in asymptomatic subgroups (stage 0) are presented. Achievements of primary selected prevention in individuals at clinical high risk for psychosis (stage 1) are summarized, along with challenges and limitations of its implementation in clinical practice. Early intervention and secondary prevention strategies at the time of a first episode of psychosis (stage 2) are critically discussed, with a particular focus on minimizing the duration of untreated psychosis, improving treatment response, increasing patients' satisfaction with treatment, reducing illicit substance abuse and preventing relapses. Early intervention and tertiary prevention strategies at the time of an incomplete recovery (stage 3) are further discussed, in particular with respect to addressing treatment resistance, improving well-being and social skills with reduction of burden on the family, treatment of comorbid substance use, and prevention of multiple relapses and disease progression. In conclusion, to improve outcomes of a complex, heterogeneous syndrome such as psychosis, it is necessary to globally adopt complex models integrating a clinical staging framework and coordinated specialty care programmes that offer pre-emptive interventions to high-risk groups identified across the early stages of the disorder. Only a systematic implementation of these models of care in the national health care systems will render these strategies accessible to the 23 million people worldwide suffering from the most severe psychiatric disorders.

Key words: Psychosis, schizophrenia, psychosis risk, clinical high risk, first episode psychosis, universal prevention, selective prevention, indicated prevention, outcomes, clinical staging

(World Psychiatry 2017;16:251–265)

Psychotic disorders such as schizophrenia are common, with 23.6 million prevalent cases worldwide in 2013[1]. One in two people living with schizophrenia does not receive care for the condition[2]. The recovery rates (one in seven[3]) and associated disability (11th cause of disability worldwide in 2013[1]) following a first episode of psychosis have not improved over the past seventy years under routine clinical care[1,3]. Although existing psychopharmacological treatments alone can reduce some symptoms, they have little impact on the outcome of the illness[4].

The annual national costs for the schizophrenia population ranged from US$94 million to US$102 billion worldwide, up to 1.65% of the gross domestic product[5]. Furthermore, risk of all-cause mortality for psychotic disorders is twice (risk ratio 2.54) that of the general population[6]. There is thus an urgent clinical and societal need for improving outcomes of psychosis.

Recent advances in research knowledge have opened new opportunities for ameliorating outcomes of psychosis during the critical periods surrounding the first episode of the illness (about 2 years before[7] and 3 years after[8] the onset). In this paper, we critically review these opportunities, summarizing the state-of-the-art knowledge and focusing on recent discoveries and future avenues for first episode research and clinical interventions.

As a conceptual framework we will adopt a revised version of the clinical staging model[9] (Table 1). We will mostly focus on non-affective psychoses, although some issues can also be applied to the other types of psychoses.

PRIMARY PREVENTION

Mental health promotion aims to promote positive mental health by increasing psychological well-being, competence and resilience, and by creating supporting living conditions and environments. It is not addressed in the present paper.

Primary prevention aims to reduce the incidence of symptoms and ultimately of mental disorders[10]. The three categories of primary prevention identified by the World Health Organization (WHO)[11] are: *universal prevention*, targeting the general public or a whole population group that has not been identified on the basis of individual risk; *selective prevention*, targeting individuals or subgroups of the population whose risk of developing a mental disorder is significantly higher than the rest of the population; and *indicated prevention*, targeting high-risk individuals who are identified as having minimal but detectable signs or symptoms foreshadowing mental disorders.

Universal prevention of psychosis

Universal primary prevention must take the form of a safe population-wide intervention that promotes normal development. Research in this area is still in its infancy, because no established pathophysiological mechanisms to be targeted have been validated[12].

A recent pioneering, randomized placebo-controlled clinical trial of dietary phosphatidylcholine supplementation was

Table 1 Revised clinical staging model for psychotic disorders and interventions for improving the outcomes of first-episode psychosis (FEP)

Clinical stage	Definition	Definition in clinical staging model	Intervention
0	Asymptomatic genetic risk	Premorbid	*Selective primary prevention*
			Improved mental health literacy
			Family psychoeducation
1a	Negative and cognitive symptoms	CHR-P	*Indicated primary prevention*
			Formal mental health literacy
			Family psychoeducation
			Active reduction of substance misuse
1b	Attenuated psychotic symptoms	CHR-P	*Indicated primary prevention*
			Family and individual psychoeducation
			Active reduction of substance misuse
			Vocational support
			Psychological therapies
1c	Short-lived remitting psychotic episodes	CHR-P	*Indicated primary prevention*
			As for 1b
			Close-in monitoring
2	Full-threshold FEP	Early full recovery	*Early intervention and secondary prevention*
			Family and individual psychoeducation
			Psychological therapies
			Active reduction of substance misuse
			Atypical antipsychotics and other medications
			Vocational rehabilitation
3a	Single relapse of psychotic disorder	Late/incomplete recovery	*Early intervention and tertiary prevention*
			As for 2, but with emphasis on relapse prevention and early warning signs
3b	Multiple relapses	Late/incomplete recovery	*Early intervention and tertiary prevention*
			As for 2, but with emphasis on long-term stabilization
3c	Incomplete recovery from first episode	Late/incomplete recovery	*Early intervention and tertiary prevention*
			As for 3a; clozapine in case of treatment resistance
4	Severe, persistent or unremitting illness	Chronicity	*Maintenance intervention*
			As for 3a-c, but with emphasis on social participation despite ongoing disability

CHR-P – clinical high risk for psychosis

conducted in a small sample of healthy pregnant women, starting in the second trimester and continuing through the third postnatal month[13]. The intervention aimed at correcting delays in cerebral inhibition that may develop perinatally, as indexed by electrophysiological biomarkers. The intervention was free of significant side effects and showed proof of concept efficacy.

Although larger studies need to be conducted to validate these initial findings, future research in this field is warranted over the next decade. Promising research candidates for the universal prevention of psychosis and the supporting evidence, which awaits future replication, are listed in Table 2.

Table 2 Candidate universal interventions for primary prevention of psychosis

Intervention	Supporting evidence	Target
Perinatal phosphatidylcholine	Randomized controlled trial[13]	Electrophysiological biomarkers of neonatal development
School-based interventions	Randomized controlled trials[14,15]	Bullying, victimization, pro-bullying attitudes, pro-victim attitudes, empathy toward victims
Fetal and neonatal N-acetylcysteine	Randomized controlled trial[16]	Biomarkers of neuroinflammation and neuroprotection
N-3 polyunsaturated fatty acids	Review[17]	Biomarkers of neuroinflammation
Vitamins A, D, B-group, folic acid	Original study, meta-analysis[18,19]	Biomarkers of neuroinflammation
Sulphoraphane	Review[20]	Biomarkers of oxydative stress
Prebiotics	Review[21]	Microbiota dysbiosis
School-based interventions	Randomized controlled trial, review[22,23]	Substance abuse
Exercise training	Original studies[24-27]	Brain plasticity, structure, connectivity, cognitive functioning

Asymptomatic genetic risk (stage 0)

The staging perspective (Table 1) provides a framework for research and conceptualization of earlier premorbid interventions to alter the developmental pathway to first-episode psychosis. Selective interventions in this stage could target parental, perinatal, social or later environmental risk factors before symptoms and help-seeking behaviour manifest[28], such as those listed in Table 3.

Although this is an exciting area for future research, currently there are no robust and effective preventive strategies to reduce the risk of psychosis in asymptomatic individuals exposed to these environmental risk factors[51]. For now, the primary viable strategy is to use the family high-risk approach (selecting offspring of individuals with schizophrenia), even though this approach will only yield roughly 10% of the individuals from these families who will develop psychosis[51].

Improving mental health literacy in these at-risk populations may represent an effective pragmatic strategy to help prevent or facilitate earlier intervention in psychosis (Table 1).

Clinical high risk for psychosis (CHR-P, stage 1a-c)

State of the art

The introduction of specific semi-structured interviews[52-54], about two decades ago[55], for the ascertainment of signs and symptoms suggestive of psychosis risk states has allowed the identification of individuals at clinical high risk for the development of psychosis (CHR-P) before full symptoms manifest[56]. These individuals are functionally impaired in comparison with matched controls at baseline[57] and have an up to 20% 2-year risk (95% CI: 17%-25%) of developing psychosis[58].

Their risk peaks in the first two years[59] and is specific for the development of psychotic disorders but not for emerging non-psychotic disorders[60,61]. However, less than half of those who will *not* develop psychosis will eventually remit (35% of the baseline cohort)[62], since persistent comorbidities (that were already present at baseline[63-65]) and functional impairment are frequently observed at follow-up[64].

Indicated interventions through specialist CHR-P provision have been recognized as an important component of clinical services for early psychosis intervention[66-68] – see, for instance, the guidelines of the UK National Institute for Health and Care Excellence (NICE)[69], and the Access and Waiting Time (AWT) standards of the UK National Health Service[67].

Conceptually, although most of CHR-P individuals (73%) would present with some comorbid DSM-IV diagnosis at baseline[63,70], the intervention is still considered preventive[71] (indicated) since these individuals are selected on the basis of having early signs or symptoms of psychosis risk.

Indicated interventions in CHR-P people may improve the outcome of first-episode psychosis through the following mechanisms: a) delayed or prevented onset of a first episode; b) better engagement with services and reduced comorbidity; c) reduced duration of untreated psychosis (DUP); and d) improved early detection and amelioration of the severity of first-episode cases (secondary prevention).

Meta-analysis of randomized controlled trials in CHR-P individuals suggests that short-term (6-12 months) psychological interventions can halve the risk of illness onset at 12 months[72]. However, the preventive effect is not sustained over a longer period of time (24 months and longer); so, these findings should be interpreted cautiously and may indicate a delayed rather than prevented psychosis onset. No trials have investigated whether long-term provision of focused interventions may result in sustained benefits. Furthermore, the three largest studies of preventive interventions in individuals at ultra-high risk for psychosis have turned out to be negative, possibly because of low power[73-75]. At the moment, there are no approved interventions that have been shown to reliably alter the long-term course of the disorder[12].

CHR-P services are effective in improving trust and engagement[76], with high satisfaction of users. Furthermore, since

Table 3 Some environmental risk factors for psychosis supported by meta-analytical level of evidence in the current literature

Type of environmental risk factor	Meta-analytical association with psychosis	Association measure type: mean (95% CI)
Parental risk factors	Parental psychosis[29]	RR: 7.87 (4.14-14.94)
	Parental affective disorder[29]	RR: 6.42 (2.20-18.78)
	Old paternal age[30]	RR: 2.22 (1.46-3.37)[a]
Perinatal risk factors	Complications of pregnancy[31-33]	OR: 2.44 (1.13-5.26)[b]
	Abnormal foetal growth and development[31,32]	OR: 3.89 (1.40-10.84)[c]
	Complications of delivery[31,32]	OR: 2.21 (1.38-3.54)[d]
	Gestational influenza[33]	RR: 1.56 (1.05-2.32)
	Season of birth[34]	OR: 1.07 (1.05, 1.08)
Social risk factors	Ethnic minority[35-37]	RR: 4.7 (3.3-6.8)[e]
	First and second generation immigrant status[38]	IRR: 2.3 (2.0-2.7)[f]
	Urbanicity[39]	OR: 2.37 (2.01-2.81)
Later risk factors	Infections[40-42]	OR: 2.70 (1.34-4.42)[g]
	Traumatic brain injury[43]	OR: 1.65 (1.17-2.32)
	Vitamin D deficiency[44]	OR: 2.16 (1.32-3.56)
	Daily tobacco use[45]	OR: 2.18 (1.23-3.85)
	Cannabis heavy abuse[46]	OR: 3.90 (2.84-5.34)
	Childhood trauma and adversity[47]	OR: 2.75 (2.17-3.47)
	Adult life events[48]	OR: 3.19 (2.15-4.75)
	Premorbid IQ[49,50]	OR: 4.78 (3.19-7.13)[h]

RR – risk ratio, OR – odds ratio, IRR – incidence rate ratio
[a]age >55, [b]gestational age <37 weeks, [c]birth weight <2000g, [d]incubator or resuscitator, [e]Black African vs. White British, [f]first generation migrants, [g]Toxoplasma gondii, [h]IQ<70. Some of these risk factors may also include a genetic component.

most CHR-P people present with comorbid disorders that are not severe enough to be accepted and treated by generic mental health services, CHR-P services may also improve these problems as well as provide vocational support and reduce family stress.

Patients who engage with CHR-P services and who will later develop the disorder show a substantial reduction of their DUP (11 days on average) compared to patients who do not present to clinical services until the first episode (approximately 1 year on average)[77]. Compared to patients accessing first episode services, patients who presented in the CHR-P stage are also less likely to require admission following the onset of psychosis (46% vs. 68%) and less likely to require a compulsory admission in the short term (30% vs. 62%)[77].

Finally, the presence of CHR-P services may have extended benefits for the identification of first-episode cases and for secondary prevention. In fact, about one-third of patients referred to CHR-P services have already developed a first episode of psychosis at the time of initial contact[78]. First-episode patients presented to CHR-P service spent fewer days in hospital (less than 17), had a shorter referral to diagnosis time (–74.5 days), a lower frequency of admission (incidence rate ratio = 0.49), and a lower likelihood of compulsory admission (odds ratio = 0.52) compared to patients who were first diagnosed by first-episode services[78]. However, these findings may be confounded by a selection bias, which is discussed below here.

Challenges and future advancements

Even assuming that an effective preventive treatment altering the course of the illness may be discovered in the next generation of interventional studies, the overall impact of treating CHR-P individuals on the outcomes of first-episode psychosis is still undetermined. This is mostly due to the fact that the potential benefits of the primary prevention during the CHR-P stage are practically limited by the difficulty to identify and treat all the individuals who are at risk of developing the disorder.

How should CHR-P individuals be recruited from secondary mental health services?

Current guidelines recommend that the CHR-P assessment should be primarily offered to individuals who are "already distressed by mental problems and seeking help for them"[79]. These individuals represent an exceptional window of opportunity for preventive interventions as they are already in contact with secondary mental health services. Unfortunately, only 5.19% of the total cases of emerging first-episode psychosis among patients

accessing secondary mental health services are detected and under the care of CHR-P services that had been well established (several years before) in the local national health system[80].

This result is highly disturbing, as it indicates that the overall real-world impact of CHR-P detection and treatment for improving the outcomes of first-episode psychosis is minimal, missing 95% of individuals who will eventually develop psychosis. Thus, it seems crucial to optimize the proportion of individuals at risk of developing psychosis who are referred to CHR-P services. Individualized risk estimation e-tools that are based on easily collectable variables have recently been developed and externally validated (www.psychosis-risk.net)[80]. Since the vast majority (91%) of patients referred to first-episode services had a first point of contact within secondary mental health care[81], the use of these tools can substantially extend the benefits of preventive interventions to most at-risk individuals and eventually result in a massive impact for the improvement of first-episode psychosis outcomes.

How should CHR-P individuals be recruited outside clinical samples?

The use of the CHR-P approach outside clinical samples or for screening purposes is not recommended, because its low ability to rule in psychosis[52] produces a substantial dilution of risk enrichment[82], leading to underpowered clinical trials[75] and questionable clinical relevance for preventive interventions[52,83-85]. For example, using CHR-P assessment in the general non-help-seeking adolescent population is associated with a 2.5-year risk of psychosis onset of 2% only[86].

At the same time, it seems important to continue exploring the usefulness of an extended use of CHR-P assessment to populations not accessing mental health services in order to improve detection of at-risk cases. Possible solutions may include the use of meta-analytical Fagan's nomogram[52] or stratification models[84] that have recently been made available to estimate the overall risk enrichment of samples undergoing CHR-P assessment.

A complementary approach may be based on the use of sequential testing methods[87]. The sequential use of screening instruments and CHR-P assessment in non-help-seeking adolescents from the general population may identify individuals who are at potential risk of developing psychosis in the following years[88]. Sequential testing is in line with the clinical staging model and can be further enhanced by front-line primary care youth mental health models developed to facilitate the access of young people from the school and community (see https://www.headspace.org.au).

Innovative strategies to identify non-help-seeking individuals at risk of psychosis can also involve the use of e-health technologies, for example based on semantic analysis of social media postings.

Can we provide stratified treatments to the CHR-P subgroups?

Future advances could also develop stratified preventive treatments targeting the different CHR-P clinical stages (a, b or c), that may have different characteristics with respect to underlying disease processes and prognosis[89]. On the basis of the increasing risk (clinical stage 1a: 3% at 2 years[58]; clinical stage 1b: 19% at 2 years[58]; clinical stage 1c: 39% at 2 years[58] and 51% at more than 3 years[90]), and symptoms severity[91] (individuals in the clinical stage 1c would formally meet the ICD criteria for a brief psychotic disorder[92]), preventive interventions for the clinical stage 1a can be supplemented by specific psychological therapies and individual psychoeducation for the clinical stage 1b.

These treatments may be further supported by a more intensive or close-in monitoring for the clinical stage 1c, which is characterized by short-lived and self-remitting psychotic episodes lasting few weeks only (e.g., less than 4 weeks)[90]. In line with the clinical staging model, the stage 1c is less severe compared to patients experiencing a first episode of schizophrenia (clinical stage 2), who do not spontaneously remit from their symptoms without antipsychotic treatment and who show substantial higher risk of relapses[90].

EARLY INTERVENTION AND SECONDARY/TERTIARY PREVENTION

Full threshold first-episode psychosis with early recovery (stage 2)

State of the art

The stage 2 encompasses the acute phase or crisis, that is characterized by florid psychotic symptoms (sustained symptoms lasting four weeks or more as suggested by the NICE Quality Standard 102[93]), followed by an early recovery phase or post-acute phase observed in the first 6-12 months following the acute episode.

Recovery is usually operationalized as concurrent clinical remission – less than mild symptoms at the Positive and Negative Syndrome Scale (PANSS) ($\leq$3), the Scale for the Assessment of Positive Symptoms (SAPS)/Scale for the Assessment of Negative Symptoms (SANS) (<3), or the Brief Psychiatric Rating Scale (BPRS) ($\leq$3), sustained for at least 6 months[94] – and functional remission (proper social functioning in the main domains of everyday life)[95]. Early interventions and secondary preventive interventions during stage 2 may improve the outcome of first-episode psychosis through the following mechanisms: a) DUP reduction; b) improvement of treatment response; c) improved well-being, functioning and social skills with reduction of burden on the family; d) treatment of comorbid substance use; e) secondary prevention of disease progression.

A long DUP is associated with poor general symptomatic outcome, more severe positive and negative symptoms, lesser likelihood of remission, and poor social functioning and global outcome, but not employment, quality of life or hospital treatment[96]. The meta-analytical correlations are small in magnitude

(r = 0.13-0.18), yet robust[96]. Since the majority of DUP is accounted for by delays in accessing early intervention services and help seeking[97], at least in the UK, it is a modifiable factor even during the clinical stage 2. Community psychosis awareness campaigns, including publicity and community engagement integrated with a specific youth mental health direct care pathway, can halve the DUP compared to detection as usual (mean 104 vs. 285 days)[97].

Beyond the impact on DUP, intervention in the clinical stage 2 can be associated with substantial improvements in treatment response. A systematic research of the literature summarizing the results of randomized controlled trials of integrated multicomponent early intervention services for patients experiencing a first episode of psychosis is presented in Table 4. The multicomponent interventions were mostly based on the comprehensive use of antipsychotics[98-100,102,105-108], individual psychological treatments[98-100,105-108], family[98-100,102,105-107] and vocational[98,99,102,105,107] support. Small trials showed minimal beneficial effects or no effects at all on clinical outcomes[99,100,110]. Larger trials showed a significant short-term (i.e., up to 24 months) improvement of treatment response under specialized integrated early interventions compared to standard community care. The improved response to the comprehensive treatments was characterized by lower disengagement from care[98,102,105]; reduction of positive[100,102,107], negative[100,102] and total[105-107] psychotic symptoms; reduced hospitalization[98,107], lower dosages of antipsychotic medications[102], and improved functioning[106].

Specialized interventions during the clinical stage 2 are associated with higher patients' satisfaction with treatment[102] and improved personal well-being[105,106], characterized by better sense of purpose, motivation, curiosity and emotional engagement[105]. These improvements translated into better quality of life[105] and greater involvement in school and work[105,107], with an overall reduced burden to the family[102]. Family interventions for first-episode psychosis are an integral component of treatment, but they can have beneficial effects even as standalone treatment, with greater 12-month improvements in family burden and caregiving experience, reductions in severity of psychotic symptoms and duration of re-hospitalizations[111].

The detrimental impact of illicit substance abuse on the long-term outcome of psychosis is well known, with a dose-dependent association[112]. Available trials confirm that it is possible to reduce substance abuse in first-episode psychosis through specialized integrated early intervention services[102]. Randomized controlled trials are directly investigating the effectiveness of a behavioural intervention for reducing cannabis use among young people receiving treatment from early intervention services[113,114].

Finally, interventions in this phase are crucial for the secondary prevention of illness progression to clinical stage 3, in particular to prevent relapse into a second episode of psychosis (3a). This is significant, because relapse interferes with the social and vocational development of individuals suffering from a first episode of psychosis, which has an impact on long-term outcomes[115].

Challenges and future advancements

Although specialized first episode services that provide a comprehensive care can significantly improve outcomes of first-episode psychosis, and their implementation is overall recommended[116], there are some significant challenges.

Are specialized integrated early intervention services effective in preventing relapses?

Despite the benefits yielded by specialized integrated early intervention services, many patients still have an increased risk of relapsing into a second episode of psychosis following an initial recovery (clinical stage 3a). Criteria for relapse vary across studies, but readmission to a psychiatric hospital is the most common definition of psychotic relapse in the existing literature[117].

Since randomized controlled trials provide the gold standard methodology for evaluating interventions for relapse prevention, we have updated an earlier meta-analysis that included only three trials investigating the risk of relapse/admission to psychiatric hospital under specialized early intervention services, compared to standard care[118]. We now include 12 trials stratified for different time points, as indicated in Table 4.

We found that mean relapse rates under treatment as usual were 14% (95% CI: 10%-20%) at 9 months, 49% (95% CI: 29%-69%) at 24 months, and 76% (95% CI: 53%-90%) at more than 10 years, while under the specialized integrated early intervention services they were 17% (95% CI: 13%-21%) at 9 months, 38% (95% CI: 14%-66%) at 24 months and 54% (95% CI: 36%-70%) at more than 10 years.

Figure 1 shows that there was no meta-analytical evidence that specialized integrated early intervention services can substantially improve the odds ratio for having a relapse compared to standard care, at any time points. These negative findings are in line with naturalistic studies, showing that about 50% of cases of first-episode non-affective psychosis relapse at least once (clinical stage 3a), while 34% have multiple relapses (clinical stage 3b). Adherence (odds ratio 2.9) and schizophrenia diagnosis (odds ratio 2.2) were the most robust predictors of the first relapse[119].

These findings are also in line with the lack of stringent evidence for a robust effect of antipsychotics on relapse prevention in the long term and with meta-analyses indicating that the overall rate of long-term recovery following a first episode of psychosis has not improved much worldwide over the past decades[3]. There is still much to be done to develop effective integrated treatments for tertiary relapse prevention in early psychosis.

Should we use long-acting injectable antipsychotics earlier?

International treatment guidelines for first-episode psychosis recommend antipsychotic medication maintenance for at least 1-2 years to prevent relapse[120]. The

Table 4 Randomized controlled trials of the effectiveness of specialized integrated early intervention services for first-episode psychosis

Study	Intervention	Control	Treatment group (N)	Control group (N)	Follow-up (months)	Outcome
Craig et al[98]	Specialized integrated early intervention (antipsychotics, cognitive behaviour therapy, family counselling, vocational help)	Treatment as usual in community care	71	73	18	No difference in relapse, reduced psychiatric hospitalization and disengagement
Kuipers et al[99]	Specialized integrated early intervention (atypical antipsychotics, cognitive behaviour therapy, family intervention, vocational help)	Treatment as usual in community care	32	27	12	No significant benefits including psychiatric hospitalization
Grawe et al[100] Sigrúnarson et al[101]	Specialized integrated early intervention (family psychoeducation and therapy, home crisis management, cognitive behaviour therapy, antipsychotics)	Treatment as usual in community care	30	20	24 168	At 24 months, reduced negative and positive symptoms; no benefits on psychiatric hospitalization or recurrences. No substantial long-term effects.
Petersen et al[102] Bertelsen et al[103] Secher et al[104]	Specialized integrated early intervention (family psychoeducation, social skills training, antipsychotics)	Treatment as usual in community care	275	272	12, 24 60 120	At 12 months, reduced hospitalization. At 24 months, improvement on positive and negative symptoms, substance abuse, treatment adherence; lower dosage of antipsychotic medication, higher satisfaction with treatment, reduced burden to the family; no effect on psychiatric hospitalization. At 60 months, many positive effects disappeared; more patients living independently. At 120 months, most positive effects had diminished or vanished.
Kane et al[105]	Specialized integrated early intervention (family psychoeducation, resilience-focused individual therapy, supported employment and education, antipsychotics)	Treatment as usual in community care	223	131	24	Reduced disengagement, greater improvement in quality of life, well-being and total psychopathology, greater involvement in work and school, no effect on psychiatric hospitalization
Ruggeri et al[106]	Specialized integrated early intervention (cognitive behaviour therapy, family intervention, case management, antipsychotics)	Treatment as usual in community care	272	172	9	Reduced total symptom severity, improved functioning and emotional well-being; no effect on psychiatric hospitalization or disengagement
Srihari et al[107]	Specialized integrated early intervention (antipsychotics, family education, cognitive behaviour therapy, vocational support)	Treatment as usual in community care	60	57	24	Reduced psychiatric hospitalization, positive and total psychotic symptoms, improved vocational engagement, no effect on functioning
Chang et al[108] Chang et al[109]	3-year specialized integrated early intervention (psychosocial interventions, cognitive behaviour therapy, antipsychotics)	2-year specialized integrated early intervention and 1-year step-down care	82	78	12	Better functioning, reduced negative and depressive symptoms and disengagement, no effect on psychiatric hospitalization
Ando et al[110]	Specialized integrated early intervention	Treatment as usual in community care	34	34	9	No effects on disengagement, functional remission, psychiatric hospitalization, self-harm, suicide attempt, social relationship

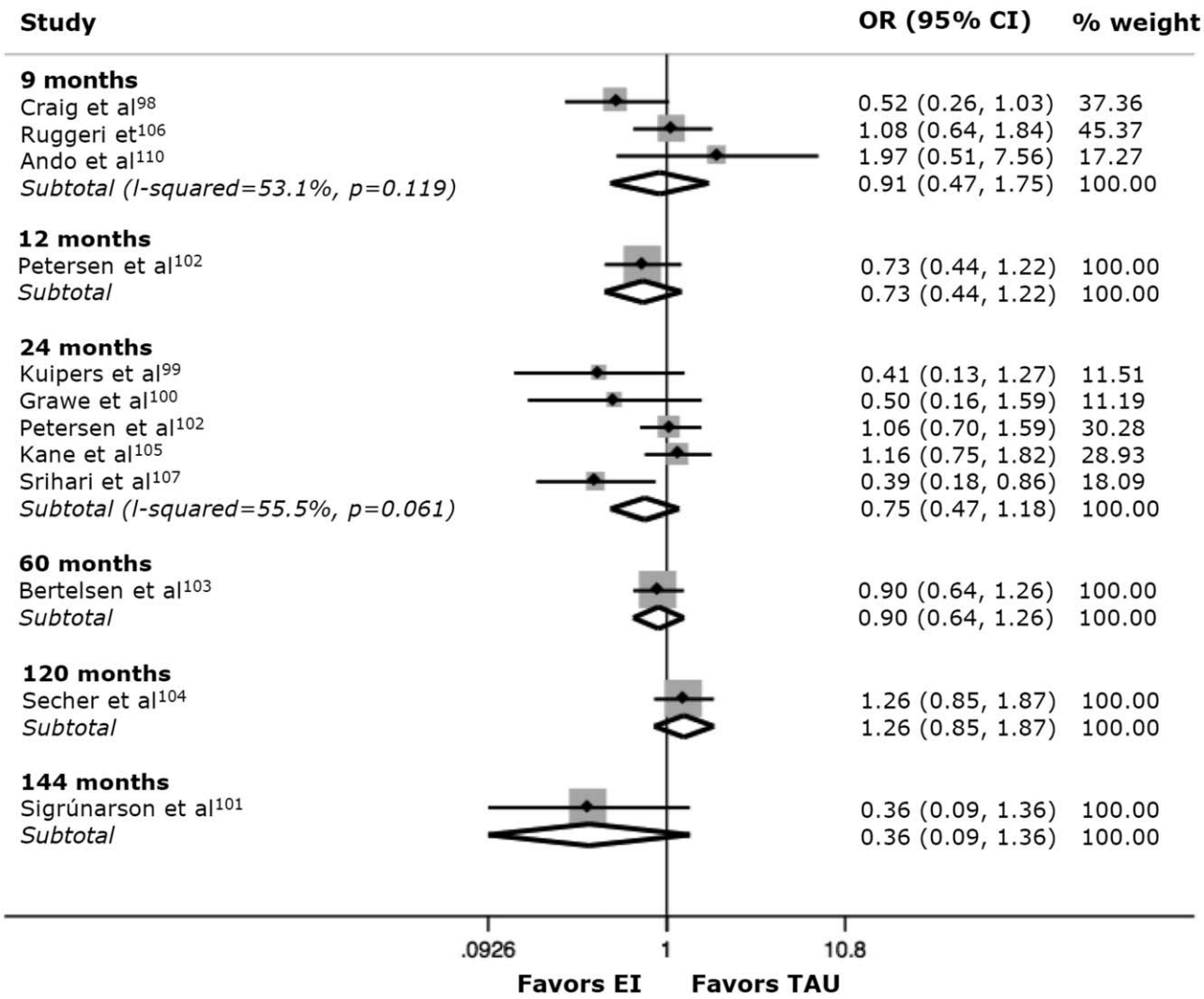

Figure 1 Meta-analytical odds for relapses (hospital readmission) with specialized integrated early intervention services (EI) compared to standard care (TAU) in the community. Odds ratios smaller than 1 indicate an association of reduced relapses with EI, while odds ratios greater than 1 indicate an association of reduced relapses with TAU. Weights are from random effects analysis.

most robust meta-analysis of randomized controlled trials of antipsychotics in first-episode patients showed 26% risk of relapse in the treatment group at 1 year, compared to 61% in the placebo group at 1 year (risk ratio = 0.47)[121].

Since antipsychotics are effective in the short term to prevent relapse, and non-adherence is a modifiable risk factor, it seems justifiable to introduce the use of long-acting injectable antipsychotics (LAIs) earlier in the treatment of psychosis, during the clinical stage 2[122]. LAIs are superior to placebo not only for the prevention of relapse but also for the reduction of symptoms in acutely ill patients with established psychosis[122].

However, seven independent meta-analyses of available randomized controlled trials, including one conducted in recent-onset psychosis (including only three trials enrolling patients with a diagnosis of psychosis within 1-5 years)[123], found no evidence that LAIs are associated with better efficacy on relapse prevention, compared to oral antipsychotics[124-129].

It is possible that randomized controlled trials enrol patient samples that are not representative of real-world clinical practice. In fact, meta-analyses of studies comparing LAIs vs. oral antipsychotics in the same patients, that better reflect real-world efficacy, found strong evidence for LAIs superiority on preventing hospital admission (risk ratio = 0.43)[130]. Furthermore, since the available trials have been mostly conducted in chronic patients or in patients with some years of active psychosis, the actual efficacy of LAIs in patients with a first episode of psychosis (clinical stage 2) is undetermined. In general, LAIs are similar to one another in terms of relapse prevention[122].

Using LAIs in first-episode patients with clear risk factors for relapse – such as a diagnosis of schizophrenia, non-adherence to oral antipsychotics, comorbid substance misuse and poor insight – may thus substantially improve outcomes of first-episode psychosis.

For how long should early intervention services be offered?

Beyond relapse prevention, most trials indicate that the benefits provided by early intervention services are attenuated over the long term[101,103,104], at more than 2-year follow-up, although these findings may be due to insufficient power. It is likely that the positive effects of intensive early treatment are sustained only if patients continue to receive specialized services (though at what intensity/frequency remains a question).

A recent trial compared a 3-year provision of specialized services versus a 2-year provision of the same. The extended year was associated with significant benefits on negative and positive symptoms, as well as on functioning[108]. This also aligns with the clinical staging model, wherein symptom resolution and clinical stabilization take place at an earlier stage followed by gradual functional improvement, which occurs later and requires substantially longer to achieve.

Discharging first-episode patients back to primary care or poor morale generic mental health services that focus heavily on patients with persistent illness, after 1-2 years of specialized early intervention care, is likely to result in the erosion of the initial advantages and gains and is thus unlikely to change their long-term recovery outcomes.

Longer-term early intervention services spanning the entire critical period of 5 years[8] are under development[131]. A subset of cases will almost certainly need longer-term expert care. In the context of competing demands and budgetary constraints, it is important to note that the costs for comprehensive specialized integrated care are exceeded by its benefits, relative to standard community care[132-134].

Schizophrenia spectrum vs. affective spectrum first-episode psychosis: does it make any difference?

Formulating a specific ICD or DSM diagnosis of psychosis at the time of the first contact with the first-episode services is challenging, because the clinical features are relatively non-specific. However, the NICE recommendation 1.3.4.3 for first-episode psychosis clearly indicates that if the patient's presentation suggests an affective rather than schizophrenia spectrum psychosis, different clinical guidelines (e.g., those for bipolar disorder or for depression) should be followed at least for psychopharmacological treatments[120].

A meta-analysis conducted in 14,484 first-episode patients, with an average follow-up of 4.5 years, found a high prospective diagnostic stability for schizophrenia spectrum psychoses (0.93; 95% CI: 0.89-0.97) and for affective spectrum psychoses (0.84; 95% CI: 0.79-0.89), which is comparable to other clinical diagnoses in medicine[135]. In line with the clinical staging model, the retrospective diagnostic stability was low for both spectra (0.60), indicating that many first-episode patients who receive a non-specific diagnosis of psychosis (e.g., psychosis not otherwise specified) will eventually develop schizophrenia or affective psychoses[135]. Therefore, having a baseline diagnosis of schizophrenia spectrum or affective spectrum psychotic disorder may still have significant clinical impacts[136].

Schizophrenia features are strong predictors of poor long-term outcomes (e.g., at 3 years[137] and 10 years[138-140]) in first-episode patients, with odds ratio ranging from 5.70 to 8.86[140]. An initial diagnosis of schizophrenia has been associated with higher risk of relapse at 3 years (odds ratio 2.7)[119]. The worse prognostic outcome of an initial schizophrenia diagnosis has been confirmed even in modern specialized integrated early intervention services that were offering state-of-the-art treatments to improve outcome for first-episode psychosis[119,140,141]. However, when communicating with patients, it may be preferable to use the broader term psychosis rather than schizophrenia, to fully reflect the possibility of plastic and heterogeneous outcomes.

For how long should we treat remitted patients with antipsychotics?

Because evidence is robust for the effectiveness of antipsychotic medication in reducing the short-term risk of relapse, it would seem reasonable to recommend medication maintenance for all first-episode individuals. However, the long-term efficacy of antipsychotics for relapse prevention is less established. Furthermore, since treatment disengagement is common early in the illness and is largely patient-driven[142], more effective alternatives could be considered[143]. Finally, there is increasing concern that cardiometabolic risk factors and abnormalities are present early in the illness, and related to the underlying mental disorder, unhealthy lifestyle and antipsychotic medications[144], as well as subtle extrapyramidal symptoms[145].

As a consequence of these considerations, the long-term use of antipsychotic medications has been recently questioned[146] and discontinuation of antipsychotic medication after 1-2 years is partially recommended by some clinical guidelines[147]. Two recent trials have investigated this issue, comparing treatment maintenance versus reduction/discontinuation strategies. In the short term (within the first 3 years), the risk of relapse was twice in the reduction/discontinuation group compared to the maintenance group[145,148]. However, in the longer term (at 7 years), the risk of relapse was comparable (62% in the reduction/discontinuation group vs. 69% in the maintenance group)[145].

Despite some important methodological limitations[136], it was additionally found that recovery and functional remission rates in the reduction/discontinuation group were twice those seen in the non-dose reduction/discontinuation group[145]. Importantly, the patients included in these trials had all experienced a clinical or functional remission that was sustained for six[145] or 18[148] months (i.e., clinical stage 2). Discontinuing antipsychotic treatment before remission is achieved (e.g., for the clinical stage 3) is associated with higher time to remission and later risk of relapse[149,150].

Overall, these findings indicate that the effect of antipsychotics is mostly symptomatic and unlikely to change the underlying course of the disorder, raising suspicion that these drugs may delay but

not actually prevent relapses[12]. In fact, longer treatment periods with antipsychotics before withdrawal are not associated with reduced risk of relapse[143], with a rapid return of symptoms in the relapse episode to severity levels similar to those in the first psychotic episode[143].

On the basis of the existing conflicting evidence, treatment reduction may be a stage 2 specific option only for the subset of patients who had achieved a clinical remission[94] and are not at high risk of relapse. The challenge would be to identify these low-risk individuals prior to considering treatment reduction[151]. Future research is thus needed to develop reliable stratification models for these patients according to the most robust risk factors for relapse: longer duration of untreated psychosis, male gender, poor baseline functioning and educational status, and a diagnosis of schizophrenia[152,153].

A recent meta-analysis indicated that the risk of relapse in patients diagnosed with schizophrenia who have achieved a clinical remission and then discontinued antipsychotic medications was 78% at 24 months and 84% at more than 36 months[90]. Accordingly, it has been suggested to exclude from treatment discontinuation/reduction strategies first-episode patients who have been diagnosed with schizophrenia at baseline[152].

However, future replication trials are required before treatment discontinuation/reduction can be safely implemented in clinical practice. A viable solution could be to use psychological treatments rather than placebo in both arms of a future discontinuation/reduction vs. maintenance trial, which may be an acceptable and effective alternative for patients who have chosen not to take antipsychotic drugs[154].

Incomplete recovery from first episode of psychosis (stage 3)

State of the art

The critical period after the onset of psychosis extends to the clinical stage 3. There are three forms of incomplete recovery: a) recovery is initially achieved but then followed by a relapse (clinical stage 3a); b) initial recovery is followed by multiple relapses (clinical stage 3b); c) premorbid functional or symptoms levels are never fully reached (clinical stage 3c).

Early interventions and tertiary preventive interventions during stage 3 may improve the outcome of first-episode psychosis through the following mechanisms: a) addressing treatment resistance; b) improving well-being and social skills with reduction of burden on the family; c) treatment of comorbid substance use; d) prevention of multiple relapses and disease progression.

The failure to respond to two different antipsychotics, at therapeutic doses and for a sufficient duration[155], means that a person meets the criteria for treatment resistance, and may thus be in the clinical phase 3c. Approximately 30% of patients with first-episode psychosis manifest a minimal response to antipsychotics[156]. Recognizing treatment resistance earlier and treating these cases with clozapine[157] at this stage could produce larger benefits in several domains of outcomes, because of the greater retention of patients' personal and social agency[114,158,159].

Early interventions that can improve the well-being, functioning and social skills with reduction of burden on the family as well as treating comorbid substance use are similar to those described for the clinical stage 2.

Although it has been suggested that acute psychotic exacerbations represent active periods of a morbid process that leads to disease progression (the "neurotoxic hypothesis of psychosis"), to date there is limited empirical evidence to support illness progression after each relapse[143]. The mechanisms of toxicity have not been described[160] and supporting evidence is conflicting[161]. On the one hand, based on limited data, times to remission are significantly longer for the second and third episodes[162]; treatment discontinuation[163] and the effective dose[164] are higher during the subsequent episodes compared to the first one (suggesting reduced effectiveness of antipsychotics when reintroduced after illness recurrence); and relapse duration (but not frequency) is associated with gray matter alterations[165]. On the other hand, patients' symptoms return to baseline with resumption of antipsychotic medication after the relapse[148], and the pattern of treatment response across single episode and multiple episodes patients is not different and highly variable[163,166]. For example, emergent treatment failure after relapse is evident in 16% of the first-episode and 14% of the multi-episode samples respectively[163,166], replicating an earlier finding that 1 in 6 patients failed to recover from each of their first four relapses, irrespective of which relapse it was[167]. Finally, a subset of patients (23%) can even be treatment resistant at the time of illness onset, even before the first relapse[168].

It is important to note that, beyond the controversies regarding disease progression after each relapse, it is clear that each relapse is a traumatic experience associated with potentially serious psychosocial and functional consequences that are impacting the quality of life of the patient and the caregiver. Unfortunately, no clear interventions have been developed and validated for the tertiary prevention of disease progression from stage 3a to stage 3b (prevention of relapse recurrences), because second relapses are not consistently associated with robust modifiable risk factors such as non-adherence[119]. Similarly, there are no approved treatments to prevent progression to clinical stage 4. Overall, these data are in line with the limited evidence for substantial protective effects of antipsychotics on relapse prevention in the long term and highlight a clear need for further prospective research elucidating the role of relapse on illness progression in early psychosis.

Challenges and future directions

A new test to identify non-response to antipsychotics and reduce delay to clozapine usage

Recent studies suggest that, among treatment-resistant first-episode schiz-

ophrenia patients, 70% never experienced any symptomatic remission from the time of their first presentation, while 30% had achieved a symptomatic remission before developing treatment resistance during the first 5 years of illness[168]. Therefore, for the majority of cases, treatment resistance could be most appropriately addressed with clozapine at an early stage of its presentation, particularly given that early treatment with clozapine is effective[157], and that worse outcomes are seen with a delayed use of the drug[169]. In standard mental health services, the mean delay in initiating clozapine is 4 years[170].

A further possibility to accelerate the use of clozapine for treatment-resistant patients may be to use a diagnostic test to predict non-response to antipsychotics. A meta-analysis of 34 studies (N = 9,460) found that a <20% PANSS or BPRS reduction at week 2 of antipsychotic treatment predicted non-response at 12 weeks, with a specificity of 86% and a positive predictive value of 90%[171]. The use of this test in early intervention services can facilitate the switch to a second antipsychotic (ideally LAIs in patients with risk factors for relapse) and therefore minimize the delay to clozapine.

Another possibility could be to identify treatment-resistant patients at baseline. Research in this field is in its infancy, but a recent study suggested that it is possible to identify specific predictors of treatment-resistant schizophrenia[172].

Can we prevent negative symptoms?

The presence of prominent negative symptoms at baseline is one of the strongest predictors of poor outcome in first-episode patients[173,174]. Negative symptoms are twice as likely to become non-responsive to treatments than positive symptoms[140]. A recent meta-analysis found that no available treatment for negative symptoms reached the threshold for robust clinically meaningful improvement[175].

Poor social functioning, disorganized symptoms and schizophrenia diagnosis are baseline risk factors that can be used to identify first-episode patients at risk of developing negative symptoms[140]. Negative symptoms are also predicted by longer DUP[176], suggesting that programmes aimed at shortening DUP might reduce the prevalence of negative symptoms and improve prognosis of first-episode psychosis[177].

LIMITATIONS OF THE CLINICAL STAGING MODEL

Staging models have been widely adopted in oncology, because stages are defined by clear pathophysiological boundaries associated with discrete changes in mortality risk and treatment choices [174,178]. On the contrary, the example of ventricular enlargements highlights the lack of utility of current neurobiological measures to inform prognosis and treatment decisions in psychosis[179]. Translation from clinical to pathophysiological staging is not yet available in psychosis.

Variation in cancer severity within a stage (e.g., tumor size or number of metastases) has fewer implications for prognosis and treatment than variation between stages. This is not the case for psychosis, where high heterogeneity and variations within each stage (e.g., stage 2)[58] play a substantial role. Additional robust evidence is needed to support the incremental clinical utility of the discrete stages proposed (e.g., from stage 3 to stage 4)[178,180].

TOWARDS AN INTERNATIONAL COORDINATED SPECIALTY PROGRAMME FOR EARLY PSYCHOSIS

In conclusion, we show here that to improve outcomes of a complex, heterogeneous syndrome such as psychosis, it is necessary to globally adopt complex models integrating a clinical staging framework and coordinated specialty care programmes[133] that offer preemptive interventions to high-risk groups identified across the early stages of the disorder[181].

It is possible to improve outcomes of first-episode psychosis using stage-specific interventions that are comprehensive[182], i.e. ranging from the universal prevention of psychosis to strategies for overcoming treatment-resistant psychosis, and transdiagnostic, i.e. spanning broader spectra during the clinical stage 1 and the psychosis spectrum during the clinical phase 2.

Although we have detailed the key clinical strategies for improving outcomes at each clinical stage, it is clear that only a systematic implementation of these cost-effective[132] models of care in the national health care systems will render these strategies accessible to the 23 million people worldwide suffering from the most severe psychiatric disorders.

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DOI:10.1002/wps.20446