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REVIEW

Intervention in at-risk states for developing psychosis

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Abstract Indicated prevention is currently one of the most promising approaches to fight the individual and societal burden associated with psychosis and particularly schizophrenia. The number of studies is still limited, yet encouraging results have been reported from pharmacological and psychotherapeutic trials. Furthermore, it has become clear that persons characterized by the at-risk criteria are already ill and do not only need preventive intervention but also treatment. As is indicated by a recent study successfully using omega-3 fatty acids for both purposes, it may be promising to develop and investigate interventions especially for the at-risk state, independent of their effectiveness in manifest disease states. An overview on the current findings and ongoing research in this area is provided.

Keywords Prevention of psychosis · Ultra-high risk · Prodrome · Basic symptoms · Early intervention

Introduction

A considerable part of patients suffering from psychosis and particularly schizophrenia still shows an unfavorable course [8]. Indicated prevention of psychosis has thus become an important strategy to fight the individual and societal burden [11, 38]. Like the concept of primary prevention, indicated prevention aims at incidence reduction, thereby replacing the deterministic by a probabilistic, risk-based concept [31]. Therefore, indicated prevention is associated with a probability to include persons, who do not need any intervention, demanding for a most careful cost-benefit consideration.

Most published intervention trials are based on the ultra-high risk (UHR) criteria. Although slightly differing in their operationalization [31], they generally involve three alternative intake criteria: attenuated positive symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS) and a combination of a genetic risk factor with a recent functional deterioration. Transition to psychosis is commonly defined by the presence of full-blown psychotic symptoms for more than 1 week, yet again, some differences occur across centers [31].

Prevention studies involving pharmacological interventions

Olanzapine ($n = 31$) and placebo ($n = 29$) were compared in a randomized, controlled trial (RCT) with a double-blind design [15]. Although the 1-year transition rate (TR) was much lower in the olanzapine group (16.1 vs. 37.9%), post hoc analysis remained at statistical trend level. Yet the small sample size reduced statistical power considerably. Interestingly, all transitions in the verum group emerged during the first 4 weeks, which may indicate a delayed pharmacological effect. The number needed to treat (NNT) was 4.5, which is considerably lower than, for example, the NNT of 14 shown for prevention of stroke or death by aspirin [9]. The 2-year follow-up results are inconclusive,

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as the sample size decreased considerably. Extrapyramidal symptoms did not differ between groups, but weight gain was statistically and clinically significant in the treatment group, a well-known problem with olanzapine and a tremendous disadvantage, particularly for indicated prevention.

An RCT within the German Research Network on Schizophrenia (GRNS) investigated amisulpride plus 'needs-based intervention' (NBI, $n = 65$) versus NBI ($n = 59$) [30]. Based on the German clinical staging approach of the at-risk state, which differentiates between an early and a late risk syndrome [32, 34], participants with a late condition, i.e. either APS or BLIPS or both, were included. Preliminary results showed a significantly lower 6-month transition rate with the antipsychotic. Conclusions, however, are limited by the open-label design of the study whose results need confirmation in a double-blind trial.

Another RCT evaluated the effects of 'specific preventive intervention' (SPI, $n = 31$), a combination of risperidone, cognitive-behavioral therapy (CBT) and NBI, in comparison with NBI ($n = 28$) [18]. Raters of intake and transition criteria and other scales but neither clinicians nor participants were blind to condition. The NBI-associated TR was significantly higher than the SPI-associated TR (35.7 vs. 9.7%) after the 6-month intervention period, but not after the subsequent 6-month observation period, during which SPI transition rate doubled; NNT was 4. The study did not allow disentangling the effects of risperidone and CBT. Yet as full adherence to risperidone was still associated with a significantly lower TR in comparison with NBI, the pharmacological part of the SPI condition seemed indeed associated with a preventive effect persisting after treatment cessation. However, more than half of the sample did not comply with SPI, and thus, unexplored moderating factors may have supported compliance effects on TR. No relevant side effects were reported, yet no standardized safety assessments had been employed. Forty-six months, on average, after study entry, the TR was 42.9% in the NBI group and 32.3% in the SPI group, but still only 9.7% in those fully adherent with risperidone during the intervention period [27]. Group differences failed to become significant. Yet the small size (69.5% of the original sample) certainly contributed to this lack of significance resulting despite a four-fold transition rate in the NBI group compared with the risperidone-adherent SPI subgroup.

A naturalistic, nonrandomized observational study followed the effects of antidepressants and second-generation antipsychotics (SGA) up to 5.5 years [6]. Medication was prescribed based on the clinicians' impression of the patients' needs. No transition emerged in the group treated with various antidepressants ($n = 25$), but 43% in the group treated with SGAs ($n = 28$), either alone or in combination with antidepressants. Yet 92% of the converted patients had been nonadherent to SGAs, stopping intake up to 20 months before transition. The one adherent subject later turned out to be clozapine-resistant (C. Correll, personal communication). Except for conceptual disorganization (SGA > antidepressant), baseline assessments were not different, but 42.9% of the SGA group was already treated with antipsychotics before, which may have mitigated initial positive scores. Thus, risk for transition may have been considerably lower in the antidepressant group from the start. Hence, this study does not allow any conclusions about differential preventive medication effects. Furthermore, with no report on side effects and possibly different baseline conditions, tolerability of medication cannot be estimated.

The authors suggested that continued antidepressant treatment may have had neuroprotective effects or may have unspecifically reduced stress levels. As also suggested by a recent file audit [7], these and other aspects like potential effects on negative symptoms make antidepressants a very interesting approach for prevention and RCTs are warranted.

Both SGAs and antidepressants are able to produce unwanted effects, particularly in adolescents [14, 19, 26]. These potential negative effects are one of the most important issues in prevention of psychosis; as even in the long term, roughly 20% of people were false positively classified as being at risk for psychosis and, consequently, would be exposed unnecessarily to an intervention targeting prevention [35].

Omega-3 polyunsaturated fatty acids (PUFAs) are a different, potentially neuroprotective approach [1]. In a double-blind RCT comprising a 12-week intervention with either omega-3 PUFAs ($n = 41$) or placebo ($n = 40$) followed by a 40-week monitoring period, a TR of 4.9% emerged in the verum condition and a TR of 27.5% in the placebo condition ($P = 0.007$); NNT was 4. Side effects were not significantly different. A just started multicenter study will hopefully confirm these findings [17].

Two other studies implying the idea of neuroprotection are awaiting full publication. Glycine, an *N*-methyl-*d*-aspartate-receptor agonist, was evaluated in a small open 8-week pilot trial. In absence of any transitions, significant improvement of different psychopathological domains was reported [42]. In an open 3-month proof-of-concept study, MRI findings in a small UHR group treated with low-dose lithium (450 mg/day) suggested a protection of hippocampal microstructure [5, 39]. This is the first study providing imaging data on neuroprotective effects in individuals at risk. However, the clinical and functional consequences need further exploration.

Prevention studies involving mainly psychological interventions

Another approach considered safe in terms of side effects is psychotherapy. In light of the vulnerability-stress-coping model [23], a basic preventive effect of CBT mediated by an increase in protective factors and a decrease in stress factors seems reasonable to assume. This is supported by findings demonstrating that the majority of UHR individuals have been shown to suffer from different 'comorbid' conditions, especially affective and anxiety disorders [36, 37]. Furthermore, potential effects of cognitive therapy on positive symptoms [13] should be more pronounced, when delusions and hallucinations are still attenuated, i.e. insight is retained.

Morrison et al. [21, 22] evaluated the preventive effects of 6-month cognitive therapy ($n = 37$) in comparison with a treatment-as-usual condition (TAU, $n = 23$). Subjects had to be neuroleptic naïve at inclusion, yet afterward, study-independent prescription of antipsychotics was not restricted. Primary outcome measure was transition rate, with symptomatic thresholds operationalized and assessed in a nonblinded manner by the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) [10]. Secondary measures of transition were 'DSM-IV diagnoses of a psychotic disorder', based on case vignettes presented to a psychiatrist blind for treatment condition, and 'prescription of antipsychotic drugs'. In terms of the primary outcome measure, 1-year TR was 6% in the cognitive therapy and 22% in the TAU group. Yet two participants of the cognitive therapy group with psychosis were subsequently excluded from analyses for being already psychotic at baseline. The NNT was 6 and thereby very satisfactory. Forty-seven percent of the original sample could be followed up for 3 years [21]. At this, only the secondary outcome criterion 'prescription of antipsychotic drugs' still yielded a result significantly in favor of cognitive therapy, yet as in the other long-term follow-ups [15, 27], sample size was only small. In an exploratory approach, using different covariates specifically targeted by cognitive therapy, this result was also repeated for the primary outcome definition. As with most of the pharmacological studies, methodological flaws complicate drawing conclusions here. However, the results of four methodologically sound studies, either ongoing [4, 20, 29] or in preparation for publication of results [28], will be very informative with regard to the differential and mixed efficacy of pharmacotherapy and psychotherapy.

On the basis of the German clinical staging model [32, 34], a study with a 12-month treatment phase compared effects of CBT ($n = 63$) in the early risk syndrome (mainly defined by Basic symptoms [12]) to supportive counseling ($n = 62$) [3]. At 24-month follow-up, transition rate to psychosis was significantly lower in the CBT condition.

Treatment approaches

The clinical syndromes defined by current criteria are commonly accompanied by several psychopathological, cognitive and functional complaints, leading to help-seeking behavior [31]. Thus, it has been suggested considering this group not only as at-risk but also as already ill [31]. Corresponding to this notion, the current proposal for the DSM-V includes a new "Attenuated Psychotic Symptoms Syndrome" [2].

Therefore, beyond prevention, treatment matters too. Olanzapine had a favorable effect on positive symptoms from week 8 to 28; however, weight gain was already a significant problem after the first 8 weeks [15, 40]. Within 12 weeks, amisulpride-treated patients showed a significant improvement of attenuated and full-blown psychotic symptoms as well as of basic, depressive and negative symptoms and of global functioning [30]. Elevation of prolactin was the only but important side effect, suggesting intensified monitoring and special caution in adolescents and young adults. Improvement of different domains of prodromal symptoms was also reported from a pilot study investigating aripiprazole over 8 weeks ($n = 15$); the most important adverse event was akathisia [41]. The preventive capabilities of the substance will be investigated in a recently started German multicenter trial comparing it to CBT and placebo [4]. Omega-3 PUFAs showed to be effective also on the symptomatic level (all PANSS scores at 12 weeks, 6 and 12 months as well as Global Assessment of Functioning scores) [1].

Worth noting are also results of a 9-month psychoeducational multifamily group treatment of UHR subjects, which led to a wide range of significant psychopathological and functional improvements [24], an approach which was conceptually supported by a study indicating an association between family problem solving style and further course in UHR patients [25].

Quo vadis prevention?

Available studies imply that an intervention can only be regarded as successful when its effects last long after cessation of this intervention. Yet an intervention with such a long-lasting effect would have to override the result of a complex interplay of genetic, epigenetic, neurodevelopmental and psychosocial factors determining the risk for and progress to psychosis. Thus, current concepts of an effective preventive measure need reconsideration.

Long-term intervention is a common strategy in conditions with longstanding risk conditions, for example, prevention of stroke. As implied in the concept of indicated prevention, however, this would certainly require strategies with a favorable cost–benefit ratio for the individuals at risk. Furthermore, recent observations indicate that at least the temporal variance of risk estimation by UHR criteria is broader than originally expected. Therefore, improved enrichment strategies or clinical staging algorithms allowing a more individualized risk classification have to be developed to ensure the homogeneity of risk necessary for prevention trials and to adapt intervention to the needs of the respective target group [16, 33].

Conflict of interest S. Ruhrmann received speaker's honoraria from AstraZeneca, Bristol-Myers Squibb, Essex and Janssen-Cilag. F. Schultze-Lutter declares that she has no conflict of interest. A. Bechdolf received speaker's honoraria AstraZeneca, Bristol-Myers Squibb and Janssen-Cilag. J. Klosterkötter received speaker's honoraria from AstraZeneca, Bristol-Myers Squibb and Janssen-Cilag, is member of the expert advisory board of Janssen-Cilag Germany and received a research grant from Bristol-Myers Squibb.

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