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Sommer, Iris; Oomen, Priscilla; Hasan, A.

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Maintenance treatment for patients with a first psychotic episode

Iris E.C. Sommer, Priscilla P. Oomen, and Alkomiet Hasan

Purpose of review
To provide an update of recent studies relevant for maintenance treatment with antipsychotic medication after a first psychotic episode (FEP).

Recent findings
Despite controversy derived from a follow-up analysis from an earlier study showing that attempted early discontinuation after remission was associated with improved long-term functioning, most other studies support better long-term outcome with continuous maintenance treatment after the first episode. However, the main question is not whether, but for how long maintenance treatment after FEP should be offered. Consistent evidence shows that withdrawal from antipsychotics increases the risk for a relapse or rehospitalization. On the other hand, maintenance treatment is associated with the risk to develop burdensome antipsychotic-induced side-effects and one should keep in mind that around 20% of FEP will not have a second episode. In this regard, the decision for maintenance treatment for periods above some months must be the result of a comprehensive risk–benefit evaluation during a shared decision-making process.

Summary
There is no replicated evidence that prognosis can be improved by discontinuing antipsychotic medication after a FEP. There is a clear need for additional studies to develop single-subject outcome predictors and to identify long-term efficacy of maintenance treatment beyond relapse (e.g. recovery).

Keywords
antipsychotics, first-episode psychosis, guidelines, maintenance treatment, schizophrenia

INTRODUCTION
Antipsychotic medication is a very effective treatment to reduce psychotic symptoms and to prevent relapses in persons with a psychosis [1,2]. A significant proportion of patients with first-episode psychosis (FEP) obtains full symptomatic remission following antipsychotic treatment as summarized in a recent meta-analysis [3]. In this meta-analysis, the pooled response rate from baseline defined as an improvement of at least 20% reduction from baseline on the Brief Psychiatric Rating Scale (BPRS) or Positive and Negative Syndrome Scale (PANSS) was 81% and for the cut-off of at least 50% change the response rate was 51.9% [3]. Importantly, this meta-analysis also showed that in drug-naïve patients, the response rate was higher than in patients with some pretreatment. A recent study confirmed this finding, showing that the more than 50% improvement was reached by 49% of antipsychotic naïve patients, whereas only 10% of the same patients when restarting the same antipsychotic after discontinuation and subsequent relapse responded with a more than 50% improvement, even when used in a higher dose [4*]. These and other findings [5] indicate that relapses reduce the likelihood to response to antipsychotic treatment following the first psychotic episode. One recently published large-scale trial showed that 56% of FEP patients achieved symptomatic remission after 4 weeks of treatment with open-label amisulpride [6]. Nonremitters received either olanzapine or were kept on amisulpride for...
an additional 6 weeks in a double-blind treatment phase. Remission rates after 10 weeks were 44% (switched to olanzapine) and 45% (continued on amisulpride) [6].

So although there is quite consistent evidence that antipsychotic medication is effective for treatment of FEP, the next question is more difficult to answer. Namely: after having achieved symptomatic remission, what should be recommended regarding dose and duration of antipsychotic maintenance treatment offered to persons with FEP? When considering that antipsychotics are highly effective in preventing psychotic relapses, that every treatment attempt after the first antipsychotic treatment has a reduced likelihood to be successful, and that at the same time maintenance treatment is associated with relevant side-effects, a comprehensive risk–benefit evaluation is needed at every stage of the treatment of FEP.

LITERATURE SELECTION STRATEGY
In order to present specific advances in the field, we selected only recent literature following a qualitative expert-based approach (Table 1). A qualitative literature search was performed following several discussions of the authors. We screened available up-to-date treatment guidelines [7–10] and recent meta-analyses. Finally, we added studies by hand search of the authors considered to be of particular relevance for this research question. Thus, the review was based on systematically searched sources, but is not a systematic review.

THE GUIDELINE PERSPECTIVE
Reviewing different treatment guidelines, no clearly discernible pattern for the duration of antipsychotic maintenance treatment can be identified. The American Psychiatric Association guidelines discuss the possibility of long-term maintenance treatment or a medication discontinuation in a period of stability (usually at least 6 months after remission) with close follow-ups and a plan of antipsychotic reinstatement with symptom recurrence [11]. The World Federation of Societies of Biological Psychiatry guidelines recommend a treatment for at least 12 months [12], the recently published German Association for Psychiatry, Psychotherapy and Psychosomatics treatment guideline [8], the National Institute for Health and Care Excellence [7], the Scottish Intercollegiate Guidelines Network [10] and the Schizophrenia Patient Outcomes Research Team [13] do not recommend a specific period for maintenance treatment after the first episode. The Royal Australia and New Zealand College of Psychiatrists recommend a period of up to 5-year treatment for service use after the first episode and a period of full recovery and being well for at least 12 months before cessation of medication should be considered [9].

The little help offered by guidelines on this topic reflects the paucity of evidence as to how long antipsychotic maintenance treatment should be offered [14]. The general recommendation to provide maintenance medication beyond the time-point of remission is based on the consistent finding that compared with placebo, antipsychotic maintenance treatment dramatically reduces the chance for relapse and re-hospitalization [2,15,16**].

RECENT DISCUSSION OF RISKS ASSOCIATED WITH MAINTENANCE TREATMENT
Despite the consistent findings of the importance of maintenance treatment for reducing relapse risk, the issue is brought up whether we may be doing patients more bad than good by prescribing them antipsychotic maintenance medication for an additional year (or more) after remission from FEP. This discussion has been fueled in principle by three lines of evidence as detailed below.
Table 1. Selective overview of recent and important studies dealing with questions of maintenance treatment in schizophrenia

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>Sample size</th>
<th>Type of study</th>
<th>Main findings</th>
<th>Main limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albert et al., 2018</td>
<td>[31*]</td>
<td>189 participants</td>
<td>Naturalistic study using secondary data from a RCT</td>
<td>Patients who discontinued their antipsychotic medication (32%) had higher cognitive scores at both baseline and follow-up compared with those who continued medication (68%). In the discontinuation group, cognition improved over the follow-up period, whereas some decline in cognition was observed in the continuation group. At baseline, participants who discontinued their medication had significantly better cognition, functioning and mental health as well as lower use of AP than those who did continue their medication. Therefore, the positive results seen in the discontinuation group might be because of a positive selection of participants with the most benign illness trajectories.</td>
<td></td>
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<tr>
<td>Alvarez-Jimenez et al., 2011</td>
<td>[5]</td>
<td>18 RCTs, 2707 participants</td>
<td>Systematic review and meta-analysis</td>
<td>Maintenance treatment was superior to guided discontinuation in preventing relapse. Neither reduction of hospital days nor a difference in social functioning was observed between groups. Trials included varied substantially in their definitions of relapse. Furthermore, the duration of follow-up of most trials was 12–18 months. Thus, findings can only be generalized to the first 2 years after treatment initiation.</td>
<td></td>
</tr>
<tr>
<td>Hui et al., 2018</td>
<td>[30]</td>
<td>178 participants</td>
<td>Double-blind RCT</td>
<td>Higher risk of poor clinical outcome in the discontinuation group compared with the maintenance group (39 versus 21%). Poor clinical outcome was defined by persistent positive symptoms of psychosis, treatment-resistant schizophrenia or death by suicide. The presence of persistent psychosis was the largest contributor to poor clinical outcome. Conclusions may not be generalizable as the cohort studied was rather homogeneous. Low comorbid substance abuse, and furthermore, a very high proportion of the patients was employed.</td>
<td></td>
</tr>
<tr>
<td>Kahn et al., 2018</td>
<td>[6]</td>
<td>446 participants</td>
<td>Open-label (phase 1 and phase 3) and double-blind (phase 2) RCT</td>
<td>In 56% of the first-episode schizophrenia patients, symptomatic remission was achieved after 4 weeks of treatment with amisulpride. Remission rates after 10 weeks were 44% (switch to olanzapine) and 45% (continued on amisulpride). Thus, switching to olanzapine did not improve clinical outcome and clozapine use could be considered after patients fail a single antipsychotic trial. The sample size in the second phase of the trial was relatively small, including 93 patients. Furthermore, whereas the second phase of the trial was double-blind, the first and third phase of the trial were open label. This might have increased the amount of remissions.</td>
<td></td>
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<tr>
<td>Kishi et al., 2018</td>
<td>[16**]</td>
<td>10 RCTs, 776 participants</td>
<td>Meta-analysis</td>
<td>The relapse rates at all time points except 1 month were significantly lower in the maintenance group compared with the discontinuation group. The discontinuation of antipsychotics for at least 2 months significantly increased the risk of relapse. However, the maintenance group was associated with higher discontinuation because of adverse events. Again, the trials included varied substantially in their definitions of relapse. Furthermore, the duration of the included studies was 1–2 years and no conclusions can be drawn on antipsychotic treatment and relapse for more than 2 years.</td>
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<tr>
<td>Kishimoto et al., 2013</td>
<td>[1]</td>
<td>23 RCTs, 4505 participants</td>
<td>Systematic review and meta-analysis</td>
<td>When comparing first-generation antipsychotics (FGAs) with second-generation antipsychotics (SGAs) within a large meta-analysis, individual SGAs do not seem to outperform FGAs regarding relapse prevention. As a group, however, SGAs were associated with reduced relapse, overall treatment failure and hospitalization. Again, an inconsistent definition of relapse was used across trials included.</td>
<td></td>
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*Note: AP = antipsychotic; RCT = randomized controlled trial; FGAs = first-generation antipsychotics; SGAs = second-generation antipsychotics.*
<table>
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<th>Study</th>
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<tbody>
<tr>
<td>Larsen-Barr et al., 2018</td>
<td>[35**]</td>
<td>105 participants</td>
<td>Cross-sectional survey study</td>
<td>Among the patients who had attempted discontinuation of antipsychotic medication, 62% reported unwanted withdrawal effects and 28% described psychotic or manic relapse during withdrawal. Having support was positively associated with success, suggesting that successful discontinuation of antipsychotic medication may be affected beneficially by patients' support network and encouragement of others.</td>
<td>Results may be affected by the relatively small sample size and people residing within in-patient units and those without internet access were not able to participate, which may have biased the population.</td>
</tr>
<tr>
<td>Leucht et al., 2012</td>
<td>[2]</td>
<td>65 RCTs, 6493 participants</td>
<td>Systematic review and meta-analysis</td>
<td>Treatment with antipsychotic medication significantly reduced relapse rates compared with placebo (27 versus 64%) and fewer patients given medication were re-hospitalized. Furthermore, limited evidence suggested better quality of life and reduced aggressive acts with antipsychotic treatment compared with placebo. However, the advantages of antipsychotic medication in terms of relapse must be weighed against their side-effects as more patients given antipsychotics experienced weight gain, movement disorders and sedation.</td>
<td>Only schizophrenia patients were included. Not representative for a general population of psychotic disorders.</td>
</tr>
<tr>
<td>Taipale et al., 2017</td>
<td>[47]</td>
<td>29823 participants</td>
<td>Register-based study</td>
<td>Use of antipsychotic medication was associated with a 50% lower risk of death compared with no use, suggesting that the effect of antipsychotic drugs on mortality is beneficial. Long-acting injection use is associated with a lower risk of death compared with the oral use of the same agent.</td>
<td>This observational register-based study lacked information in order to adjust for important known risk factors for premature mortality and validate causes of death.</td>
</tr>
<tr>
<td>Taipale et al., 2018</td>
<td>[56]</td>
<td>70969 participants</td>
<td>Register-based study</td>
<td>Evidence was provided on the effectiveness of long-acting injection use and clozapine over other antipsychotics. LAIs were associated with lower risk of psychiatric and all-cause hospitalization than oral antipsychotics, in both chronic and first-episode patients with schizophrenia.</td>
<td>This observational register-based study lacked data on clinically important outcomes in addition to hospitalization.</td>
</tr>
<tr>
<td>Takeuchi et al., 2018</td>
<td>[4*]</td>
<td>130 participants</td>
<td>Observational study</td>
<td>Findings suggest an association between relapse in schizophrenia and increased treatment resistance. All participants took the same antipsychotic at the second episode compared with the first episode, although with the second episode doses ended up significantly higher than those in the first episode. General and core symptom improvements were more rapid and greater in the first episode than the second episode. Furthermore, the majority of patients achieved positive symptom remission and 20% response in both the first and second episodes, with a faster attainment of this during the first episode.</td>
<td>Pill counts were used to measure nonadherence to medication, which may have underestimated nonadherence. Furthermore, important clinical information was lacking, for instance the duration of untreated psychosis, antipsychotic dose at each visit, reasons for nonadherence. Blinding was not applied.</td>
</tr>
<tr>
<td>Study</td>
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<tr>
<td>Thompson et al., 2018</td>
<td>[15]</td>
<td>7 RCTs, 520 participants</td>
<td>Systematic review and meta-analysis</td>
<td>A greater risk of relapse was demonstrated in the discontinuation groups (53%) versus the maintenance treatment groups (19%). A lower risk difference was showed with admission to hospital as main outcome.</td>
<td>Only two studies reporting on functional outcome were included, and therefore, no specific conclusion could be drawn with concern to functional outcome. Patients with a psychotic disorder, not exclusively schizophrenia patients. Relatively small number of studies and limited power of meta-analysis.</td>
</tr>
<tr>
<td>Tiihonen et al., 2018</td>
<td>[46**]</td>
<td>8719 participants</td>
<td>Observational study using population-based register data</td>
<td>Continuous use of antipsychotics for up to 20 years was associated with lower mortality than no use of antipsychotics. The lowest risk of re-hospitalization or death was observed in patients treated with antipsychotic drugs continuously, followed by patients who discontinued medication immediately after discharge from hospital treatment. Increased risks were observed for later antipsychotic discontinuation, that is, the later the antipsychotic drug is discontinued, the greater the risk of treatment failure.</td>
<td>This study used population-based register data, and lacked certain important clinical information. No information on medication adherence was provided, nor was there information available about whether discontinuation of antipsychotic use was suggested or guided by the treating physician or whether it was patient’s own decision to discontinue.</td>
</tr>
<tr>
<td>Wunderink et al., 2007</td>
<td>[29]</td>
<td>131 participants</td>
<td>RCT</td>
<td>Higher relapse rates were observed in the discontinuation group compared with maintenance treatment (43 versus 21%). There were no advantages of discontinuation antipsychotic medication observed regarding functional outcome. Of patients who received the discontinuation strategy, only 20% successfully discontinued, recurrent psychotic symptoms caused another 30% to restart antipsychotic drugs and the remaining patients could not discontinue their medication at all.</td>
<td>The open nature of the design may have biased the results and may have led to a more conservative treatment strategy in patients assigned to the discontinuation condition. The definition of remission in this study was based on positive symptoms only, making it difficult to compare results with studies that used a multidimensional definition of remission.</td>
</tr>
<tr>
<td>Wunderink et al., 2013</td>
<td>[28]</td>
<td>128 participants</td>
<td>RCT</td>
<td>Significantly higher recovery rates were shown in patients who received dose reduction compared with those who received maintenance treatment. Furthermore, symptom remission did not significantly differ between groups but greater functional recovery was observed in the dose reduction group.</td>
<td>The original randomized treatment allocation was not completely retained during the 5-year follow-up. Mean doses of antipsychotics were only slightly lower in the discontinuation group compared with the standard care group during follow-up. The differences in functional outcome between groups could be explained by the baseline difference (although not significantly) between groups in occupational status and diagnostic category. The absence of rater blindness may have biased the results concerning functional outcome in favor of the discontinuation strategy.</td>
</tr>
<tr>
<td>Zhu et al., 2017</td>
<td>[3]</td>
<td>17 RCTs, 3156 participants</td>
<td>Systematic review and meta-analysis</td>
<td>Response rates of first-episode patients with schizophrenia to antipsychotics are high (81.3% showed a reduction in PANSS or BPRS of 20%, and 51.9% showed a reduction in PANSS or BPRS of 50% from baseline). Better treatment response was seen in female patients, more severely ill patients, drug-naïve patients and patients with a short duration of illness.</td>
<td>Response data of several studies had to be imputed, which may have resulted in underestimation or overestimation of values. Possible placebo effects could not be taken into account, as no placebo-controlled trial was included.</td>
</tr>
</tbody>
</table>
First, apart from the well-known side-effects of antipsychotic treatment (e.g., extrapyramidal, metabolic, anhedonia, cardiac, and sexual side-effects) the finding of a potential antipsychotic-associated brain volume loss has been described as an additional harmful effect of antipsychotics based on the correlation of brain-volume loss and cumulative antipsychotic dosage [17–20]. The ENIGMA meta-analysis [19] showed an association between brain volume loss and cumulative antipsychotic drug use. Yet, as these data are based on naturalistic longitudinal studies, bias cannot be completely ruled out. Moreover, one meta-analysis showed that psychotic patient groups without any exposure to antipsychotics also had volume loss and one review on very early studies from the preantipsychotic area also confirmed brain volume loss in schizophrenia without antipsychotic treatment [21,22]. Finally, the relationship of the group-level findings of an antipsychotic-associated brain volume loss and the individual outcome or the significance of these findings with regard to established side-effects is not clear. This topic is still a matter of debate and more research, especially studies using a randomized design, is needed.

**DISEASE COURSE WITHOUT ANTIPSYCHOTIC TREATMENT**

A second line of evidence relevant for maintenance treatment after FEP is the question how many patients will only have one episode in their lives and how these patients can be recognized. Dependent on the follow-up period, it is assumed that ~10 to ~25% of the FEP only have one episode [23–26], with heterogeneous courses, dependent on many therapeutic, psychosocial, environmental and individual factors. These studies support the argumentation that at least part of FEP-remitted patients does not need maintenance treatment. However, it is important to note that the definitions of psychosis and schizophrenia differ across studies. Despite promising developments in precision psychiatry [27], no single-subject predictors for FEP are available to differentiate those patients who will not have a second psychotic episode from those who will, and thus may be in need of maintenance antipsychotic treatment. As long as it is not possible to predict the risk for a second psychosis after a FEP, it has been discussed to be critical to prescribe antipsychotic maintenance treatment, knowing that some one in five patients may receive treatment without a clear beneficial effect.

**GUIDED DISCONTINUATION TRIALS: LONG-TERM OUTCOME**

A third line of evidence that fueled the discussion regarding the risks and benefits of maintenance treatment stems from an influential Dutch study that re-contacted participants of a 2-year randomized controlled trial (RCT) 5 years later [28]. The original study [29] selected FEP patients who had obtained full remission within 6 months and who had shown no signs of relapse for another 6 months. From these, half of them were randomized to an attempt to discontinue medication, whereas the other 50% continued on antipsychotic medication at the same dose. However, it is important to note that only 20% of participants in the discontinue arm really stopped medication. Another 30% reduced dose, whereas 50% of the discontinue-arm participants could not reduce dose and continued on similar levels of antipsychotic medication (e.g., similar to the continuation arm). At the end of the 2 years study, relapse rates were higher in the discontinue arm as compared with the maintenance arm, whereas levels of functioning were not different among groups [29]. The follow-up 5 years after the end of study was able to interview 80% of the initial group [28], which is remarkable. Among those who could be re-contacted, the mean daily dose of haloperidol equivalents in the original discontinue group was 2.3 mg, whereas that of the original maintenance group was 3.5 mg. Of the 17 patients who initially completely discontinued medication, 11 were still medication-free after 7 years. The difference in relapse rates was no longer significant and now, the level of functioning was significantly higher in the discontinue group, with 46% achieving functional remission, against 20% in the original maintenance group [28]. This finding has fueled many vivid discussions, in which this study has often been interpreted to suggest that discontinuation is the preferred treatment after a FEP. However, this interpretation is not straightforward, as 80% of the discontinue arm actually remained on antipsychotics. Rather, this study may suggest that a low antipsychotic dosage facilitates functional recovery more than higher ones. However, there is more to this study than just the potential advantages of a dose reduction. There is also a learning experience for those who had a guided gradual dose reduction, then had a relapse and re-started on antipsychotic medication. This learning experience may have increased insight into the use of antipsychotics and increased medication adherence. One could speculate that the people in the continuation arm, who did not have this experience, also tried to discontinue, but at a later stage and without the help of the research team, which could have put them at a disadvantage. Yet, this study probably succeeded to find those 20% who will not develop a second psychosis, namely the ones who did well with the discontinuation and remained medication free.
A recent study with a related design performed in Hong Kong has re-contacted patients who participated in another 2-year RCT comparing maintenance to discontinuation after a FEP [30]. In the original study, patients were treated double blind with either maintenance treatment quetiapine (mean dose 400 mg) or discontinuation of medication. In contrast to the Wunderink study, all patients in the discontinuation arm actually stopped antipsychotic treatment. Similar to the Wunderink study in 2007, after 2 years relapse rates were higher in the discontinuation group. After 8 years, follow-up data of 80% of the initial study group (interview or chart review) was available. In this study, findings were very different as the risk for poor outcome, defined by persistent positive symptoms of psychosis, treatment-resistant schizophrenia or death by suicide, was significantly higher (39%) in the original discontinuation group, versus 21% in the maintenance group. Also, suicide rates were higher in this group (4 versus 2%). Important differences between the two studies are that the Dutch study was open-label and only 20% truly discontinued medication in that arm, as the Hui et al. study had a true discontinuation group. Despite these and other methodological differences, the completely opposite findings of these studies are remarkable, and call for further replication work.

Finally, data from the naturalistic OPUS II trial indicates that maintenance treatment may have negative effects on cognition, as patients who discontinued antipsychotic medication showed improvements in different cognitive domains. Schizophrenia patients (n = 189) were tested after 1.5 years of treatment with antipsychotics (baseline) and 3.5 years later (follow-up). Patients who discontinued their medication had higher levels of cognitive functioning in all domains at baseline, as well as global cognition. During follow-up, those patients who discontinued antipsychotic medication (32%) improved significantly more than those who remained on antipsychotic medication (68%) during the follow-up on both global cognition and several subdomains [31*].

**CONTINUOUS VERSUS INTERMITTENT MAINTENANCE TREATMENT**

In order to reduce the side-effect burden by reaching lower dosages and to identify patients with only one psychotic episode, the intermittent treatment strategy for maintenance treatment has been frequently used. Several recent meta-analyses have compared continuous maintenance treatment versus intermittent treatment and concluded that intermittent treatment is inferior [32,33], although intermittent treatment was superior to placebo treatment [33].

However, a study from 2002 adds an interesting perspective to this meta-analytic perspective. This study consists of a pooled analysis of different samples and compared different maintenance treatment strategies in 363 schizophrenia patients (115 FEP, 248 with a relapsing disease course) in an open outpatient setting after a 3-month stabilization phase over a period of 2 years. Three different strategies were compared: continuous maintenance treatment with at least 100 mg chlorpromazine equivalents per day; prodrome-based-intervention (step-by-step discontinuation, 50% every 2 weeks, re-introduction of antipsychotic treatment as soon as prodromal symptoms occurred) and crisis intervention (step-by-step discontinuation, 50% every 2 weeks, complete withdrawal of antipsychotic, antipsychotic were only reinstalled after a full relapse) [34]. Patients with a relapsing disease course had the best outcome following the maintenance treatment strategy (relapse rates 20%), whereas FEP benefit from the maintenance strategy (relapse rates 38%) and to the same extent from the prodrome-based intervention (relapse rate 42%). The complete antipsychotic withdrawal strategy resulted in 2-year relapse rates of 67% in FEP and 78% in multiphase schizophrenia [34]. However, irrespective of the strategy, we must consider that most schizophrenia patients try to discontinue antipsychotics without any support, but that a guided and supported dose reduction or even withdrawal attempt is more likely to succeed [35**].

**EARLY INTERVENTION SERVICES FOR FIRST PSYCHOTIC EPISODE**

The management of FEP is complex and obviously no single strategy alone can be considered to be more effective than a complex intervention with, for example, evidence-based antipsychotic treatment, psychotherapy, family intervention, supported employment and assertive community treatment [5]. The superior efficacy of complex early intervention services in preventing, for example, treatment discontinuation or re-hospitalization has been shown in several meta-analysis [5,36,37].

**THE MORTALITY DISCUSSION**

Patients with schizophrenia have an increased risk for premature death and this excess mortality was associated with reduced life expectancy of ~7–25 years [38–45]. Looking at the disease course, one could conclude that within the first years after FEP, risk for suicides are high, but that then somatic comorbidities account for the excess mortality, especially cardiovascular disease. However, recent
studies using the Scandinavian birth cohort data added some important new aspects to the mortality discussion in schizophrenia.

Although RCTs are better able to control for confounds, given their randomization procedure, they are often flawed by high drop-out numbers and strong selection bias. Registry studies, for example, those derived from the Scandinavian Birth Registers, can provide compensatory evidence, as randomization is lacking, but sample size is large and follow-up period may be very long with the cohorts remaining intact. In 2018, Tiihonen et al. [46**] provided controversially discussed data on the association between maintenance antipsychotic treatment and mortality. He showed that patients who continued antipsychotic medication had the lowest mortality rates after 16.4 years follow-up, whereas mortality after discontinuation of antipsychotic medication rose to 174–214% [46**]. It is a remarkable finding, given the increased risk for somatic side-effects associated with antipsychotic medication use. In the groups who discontinued medication, early discontinuation had lower mortality than late discontinuation. This difference may be attributable to the 15–20% of FEP patients who will never relapse without medication, a minority that is absent after a second or third psychotic episode. Another publication from the same cohort showed in N = 29,823 in total (N = 4603 in the incident cohort) that during a mean follow-up period of 5.7 years, continuous treatment with long-acting antipsychotics reduces the risk of death by ~30% compared with oral treatment [47]. These findings align well with an earlier study from Kiviniemi et al. [48] who used the Finnish birth registry and showed lower mortality in patients on second generation antipsychotic medication, with lowest mortality for patients on clozapine. Remarkably, not only mortality from suicide was decreased but also cardiovascular mortality, while clozapine is probably the strongest inducer of metabolic syndrome [48].

Turning our gaze again to the high rates of suicide and self-harm in first-episode patients, another large-scale cohort study based on the data from five health systems should be discussed. Simon et al. [49**] showed that compared with general outpatients, patients with FEP had a relative hazard of death of 34.93 [95% confidence interval (CI) 8.19–149.10] for self-inflicted injury or poisoning. However, because of inherent low power, meta-analysis could only show a numeric but not statistical significant superiority of antipsychotic treatment for suicidality [2]. Yet we know that being psychotic is one of the strongest predictors for suicide attempts [50] and we can hence deduce that keeping patients in long-term remission will likely reduce suicide rates.

ONGOING STUDIES

Regarding antipsychotic maintenance treatment and withdrawal in FEP, the most complex issue is functional outcome (or even more complex: the dimension of recovery), which showed controversial results in the available studies. Several new long-term follow-up RCTs are underway to provide additional information on this knowledge gap, such as the TAILOR trial in Denmark [51], the UK-based RADAR study [52], the REDUCE trial in Australia [53], the ‘Guided Dose Reduction Trial for Patients with Remitted Psychosis-Study’ from Taiwan [54] and the HAMLET study from the Netherlands [55].

CONCLUSION

There is strong and consistent evidence from randomized-controlled trials and high-quality meta-analyses that relapse rates are largely reduced by antipsychotic maintenance therapy. The findings regarding mortality based on registry studies without randomization or matching, but with high sample sizes and very long follow-up point into the same direction: a clear advantage for those on antipsychotic maintenance therapy. Regarding long-term functional outcome, replication (or nonreplication) of the Wunderink study [28] that showed long-term benefits of an attempt to discontinue antipsychotic medication is needed urgently. A related study from Hong Kong showed advantages for the continuation arm [30].

Although on a group level, the evidence for advantages of maintenance treatment clearly outweighs evidence for early discontinuation, there will always be a subgroup of about 20% of FEP patients who obtain antipsychotic medication without a need for it. Perhaps, until reliable single-subject outcome predictors have been developed or the new RCTs show other treatment strategies, a guided gradual discontinuation of antipsychotics with a close monitoring of psychopathology is the only way to single out those that really do not need maintenance treatment. As a consequence, we could think of a standard guided discontinuation attempt under tight supervision for all FEP in remission so that we will not be treating patients with antipsychotic medication who have no need for it. Unfortunately, this paradigm comes at the cost of increased relapse risk, risk for nonresponse to restarted antipsychotic and possibly increased suicide risk. A difficult decision.

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Conflicts of interest
I.S. received research support from Janssen and from Sunovion and is consultant to Gabapentin. P.O. declares that she has no conflict of interest. A.H. is co-editor of the German (DGPPN) Schizophrenia treatment guidelines and first-author of the WFSBP schizophrenia treatment guidelines. He has been on the advisory boards, and has received speaker fees from Janssen-Cilag, Lundbeck and Otsuka.

REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
- of outstanding interest


Study showing that despite a dose increase in the second episode, the likelihood to response is reduced by a relapse in first episode schizophrenia patients.


17. New meta-analysis showing that maintaining antipsychotic treatment for up to 2 years prevented relapses and that discontinuation of antipsychotics for more than 2 months significantly increased the risk of relapse in first-episode psychosis.


22. Delisi LE. The concept of progressive brain change in schizophrenia: implications for understanding schizophrenia. Schizophr Bull 2008; 34:312–321.


31. Naturalistic study showing that discontinuation of antipsychotic treatment was associated with better cognitive functioning.


Data from a nationwide register showing that the risk of relapse after antipsychotic discontinuation does not decrease as a function of time during the first 8 years and that maintenance treatment is associated with a reduced mortality.
