FULL-LENGTH ARTICLE

Predicting first-episode psychosis patients who will never relapse over 10 years

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Background. Although relapse in psychosis is common, a small proportion of patients will not relapse in the long term. We examined the proportion and predictors of patients who never relapsed in the 10 years following complete resolution of positive symptoms from their first psychotic episode.

Method. Patients who previously enrolled in a 12-month randomized controlled trial on medication discontinuation and relapse following first-episode psychosis were followed up after 10 years. Relapse of positive symptoms was operationalized as a change from a Clinical Global Impression scale positive score of <3 for at least three consecutive months to a score of ≥3 (mild or more severe). Baseline predictors included basic demographics, premorbid functioning, symptoms, functioning, and neurocognitive functioning.

Results. Out of 178 first-episode patients, 37 (21%) never relapsed during the 10-year period. Univariate predictors (P≤0.1) of patients who never relapsed included a duration of untreated psychosis (DUP) ≤30 days, diagnosed with non-schizophrenia spectrum disorders, having less severe negative symptoms, and performing better in logical memory immediate recall and verbal fluency tests. A multivariate logistic regression analysis further suggested that the absence of any relapsing episodes was significantly related to better short-term verbal memory, shorter DUP, and non-schizophrenia spectrum disorders.

Conclusions. Treatment delay and neurocognitive function are potentially modifiable predictors of good long-term prognosis in first episode psychosis. These predictors are informative in that they can be incorporated into an optimum risk prediction model in the future, which would help with clinical decision making regarding maintenance treatment in first-episode psychosis.

Key words: schizophrenia, early psychosis, relapse, long-term follow-up, predictors

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Introduction

Relapse constitutes a major problem in managing patients with psychotic disorders, with up to 80% of patients relapsing within five years following illness onset (Robinson et al. 1999). Meta-analysis shows that the risk of relapse was up to over 90% by two years following first episode psychosis (Zipursky et al. 2014). Relapse can cause substantial or even irreversible damage, particularly in young patients during the most productive period of their lives. Maintenance antipsychotic treatment for a considerable period of time is often required to prevent symptom recurrence. In first episode schizophrenia patients whose antipsychotics are discontinued (stepwise), those responding well to antipsychotics treatment had a greater risk of relapse (Gaebel et al. 2016). Longitudinal studies have revealed that around 20% of patients will not relapse after their first episode of psychosis (Shepherd et al. 1989; Linszen et al. 2001). However, not much long-term data exist to help characterize this subgroup of patients who do not relapse. The successful identification of factors predicting this subgroup can help tailor a better treatment approach in relapse prevention, in conjunction with maintenance antipsychotic treatment.

Few studies have examined the proportion and predictors of first-episode psychosis (FEP) patients who do not relapse in the long term. In a naturalistic follow-up study, Alverez-Jimenez et al. (2011) found that 16.5% of FEP patients did not relapse during the 7.5-year follow-up period, and that they are characterized by having a duration of untreated psychosis (DUP) <60 days, displaying more rapid response to antipsychotic treatment, and being less likely to have parental loss at baseline (Alverez-Jimenez et al. 2011). However, other important predictors such as neurocognitive functioning were not explored. The study has a dropout rate of up to 66% at follow-up, rendering generalizability to all psychosis patients difficult. Furthermore, relapse was retrospectively recalled by patients during the follow-up assessment, which may have introduced a bias towards recalling only more severe episodes and ignoring less “dramatic” ones, resulting in an underestimated rate of relapse-free patients. In another study of FEP patients who were randomized to an 18-month dose-reduction trial

following symptomatic remission, Wunderink et al. (2013) found that 34.9% of patients did not relapse during a 7-year period, but no predictors of relapse were reported.

This was a 10-year follow-up study of patients who were previously enrolled in a 12-month randomized controlled trial (RCT) on medication discontinuation and relapse following complete resolution of positive symptoms from FEP (Chen et al. 2010). Data from the RCT showed that the Kaplan-Meier estimate of the risk of relapse at 12 months nearly doubled in the placebo group (79%) compared to the maintenance group (41%) (Chen et al. 2010). In this 10-year follow-up study, we examined (1) the proportion of patients who did not relapse over the 10 years, (2) the potential baseline predictors of not relapsing, including socio-demographic information, symptoms, functioning, as well as neurocognitive functions, and (3) the clinical and neurocognitive outcome correlates of this subgroup of relapse-free patients.

Methods

Study design

Across the Hong Kong Special Administrative Region of approximately seven million people, specialized teams of the Early Assessment Service for Young People with Psychosis (EASY) provide assessment and treatment for patients with FEP (Chen, 2004). Between 2003 and 2005, 178 FEP patients with complete resolution of positive symptoms were randomized to receive either quetiapine (400mg/d) or placebo for 12 months (ClinicalTrials.gov Identifier: NCT00334035) (Chen et al. 2010). Upon completion of the 12-month RCT, patients continued to receive naturalistic regular care at general adult out-patient psychiatric clinics. Between November 2013 and December 2014, this cohort was followed up prospectively after 10 years to assess their clinical outcomes, including persistent positive symptoms, requirement of taking clozapine, and suicide (ClinicalTrials.gov Identifier: NCT01926340) (Hui et al. 2018). The current study focused on examining the long-term outcome of relapse.

This study was approved by the institutional review boards at each site, and carried out in accordance with Good Clinical Practice and the Declaration of Helsinki. All participants provided written informed consent.

Participants

Included participants had a diagnosis of schizophrenia or non-affective psychosis (schizophreniform disorder, schizoaffective disorder, brief psychotic disorder, or psychosis not otherwise specified) (DSM-IV) (APA, 1994), were aged 18-65 years, had been treated with antipsychotic drugs continuously for at least one year, had good medication compliance (missed <50% of their medication, missed <50% of their clinic visits, or had no history of medication discontinuation), and had no history of relapse (defined as no increase of positive symptoms of psychosis requiring admission to hospital or adjustment of medication). Patients had to be free of positive symptoms of psychosis for at least 8 weeks as assessed using (1) five Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987) items: delusions, conceptual disorganization, hallucinations, suspiciousness, unusual thought content, and (2) the Clinical Global Impressions (CGI) scale (Guy, 1976) with a score of 2 (borderline or questionable) or less. Exclusion criteria were diagnosis of drug-induced psychosis, treatment with clozapine, mood stabilizing medications (lithium, valproate or carbamazepine) or depot medication, and a risk of suicide or violence.

Diagnosis at follow-up was determined using the best-estimate consensus approach with all sources of information available, including the validated Chinese version of the Structured Clinical Interview for DSM-IV (So et al. 2003), medical records, and history from research assistants during face-to-face interviews. Two experienced psychiatrists reached a consensus in the diagnosis for each subject.

Outcome measures

To obtain the outcome measures, research assistants at Master's level carried out direct face-to-face interviews with patients at 10 years, and extracted monthly data using medical records and the Health Authority Clinical Management System over the entire follow-up period. Raters were blinded to the randomized trial assignment and the follow-up status of the participants.

Relapse was defined as the re-emergence or exacerbation of positive symptoms, as operationalized by a change from CGI positive (Haro et al. 2003) scores <3 for at least three consecutive months to a score of ≥3 (mild or more severe) (Haro et al. 2011; Chan et al. 2015). Relapse was assessed monthly using medical record review ratings of CGI positive symptom severity scores from the start of the RCT until the end of the 10 years in all patients. The CGI-positive has a rating from 1 (normal), 2 (borderline), 3 (mild), to 7 (most severely ill). For each relapse episode, we recorded the start and end dates (duration), and whether the event required hospitalization. Weekly consensus meetings were conducted among a clinician and research assistants during the data collection period for quality assurance and for resolving ambiguity in ratings. To ensure consistency in ratings, the CGI-positive was rated from eight independent medical records (i.e. not those cases recruited into the current study). Good agreement was found among the three raters, with an intra-class correlation of 0.7.

To validate the definition of relapse using CGI-positive, we compared the concordance between the relapses derived using CGI-positive with those using the "remission/relapse" definition in the abovementioned inclusion criteria. The latter was operationalized as meeting the following criteria using medical record reviews: (1) at least one of the following in the PANSS scale: delusions >3, conceptual disorganization >4, hallucinations >3, suspiciousness >5, or unusual thought content >4, and (2) scores >3 and >5 in the CGI severity of symptoms and CGI improvement scales respectively. There was excellent agreement between the two relapse definitions (κ=0.842, P<0.001).

Instead of targeting a few specific positive symptoms in defining relapse (as is the case in PANSS), the current CGI-positive definition focuses on the overall severity of the patient's positive symptoms at the time of assessment. This approach is more

relevant and applicable to data extraction using medical record reviews, given that not all clinicians provide detailed psychopathology, but instead provide an overall description of the psychotic symptoms of patients. In addition, compared to retrospective recall of relapses from patients over the past 10 years (Alverez-Jimenez et al. 2011), the current medical record review of positive symptoms of relapse using CGI-positive would minimize the chance of underestimation of any relapse episodes, and ensures that relapse of positive symptoms to a mild or more severe level are all included.

Other outcome measures included information on marital status, diagnosis, antipsychotic treatment, and medication adherence. Positive and negative symptoms were assessed using the PANSS, the Scale for the Assessment of Positive Symptom (SAPS; Andreasen, 1984), and the Scale for Assessment of Negative Symptoms (SANS; Andreasen, 1983). Depressive symptoms were assessed using the Calgary Depression Scale for Schizophrenia (CDSS; Addington et al. 1992). Insight into the illness was measured by the abridged Scale to Assess Unawareness of Mental Disorder (SUMD; Amador et al. 1994). Side effect was assessed with the Simpson-Angus Scale (SAS; Simpson et al. 1970), the Abnormal Involuntary Movement Scale (AIMS; Guy, 1976), the Barnes Akathisia Rating Scale (BARNS; Barnes, 1989), and the Udvalg for Kliniske Undersøgelser (UKU; Lingjaerde et al. 1987). Functioning was assessed using the Social and Occupational Functioning Assessment Scale (SOFAS; Goldman et al. 1992) and the Strauss and Carpenters' scale (Strauss & Carpenter, 1972). Direct interviews were performed with 142 out of the 178 patients at 10 years.

Baseline predictor measures

All potential baseline predictors were evaluated at entry to the RCT, where all patients had complete resolution of positive symptoms for at least one year following their first episode of psychosis. Baseline variables included gender, age, years of education, employment, marital status, diagnosis (schizophrenia spectrum disorders:

schizophrenia, schizophreniform disorder and schizoaffective disorder vs. non-schizophrenia spectrum disorders: brief psychotic disorder and psychosis not otherwise specified), and treatment received during the RCT (quetiapine vs. placebo).

Premorbid functioning was assessed using the Premorbid Adjustment Scale (PAS; Cannon-Spoor et al. 1982). The same symptoms, insight and functioning assessments (see above in outcome measures) were used. DUP was assessed using the Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS; Häfner et al. 1992).

Neurocognitive functions assessed were as follows: Information, Arithmetic, Digit Span (forward and backward), Digit Symbol, Block Design, Trail Making Test (response time difference between the two tasks), Letter Number Span (the highest level attained), Logical Memory Test (total number of correct immediate and delayed recalls), Visual Patterns Test (the highest level attained), Semantic Fluency Test (total number of correct animals reported in one minute), and the Modified Wisconsin Card Sorting Test (total number of perseveration errors). The total number of times the patient blinked during two minutes of relaxation was also recorded.

Statistical analysis

All statistical analyses were carried out using IBM® SPSS® Version 24.0. To examine the potential baseline predictors (independent variables) for patients who never relapsed over the 10 years (dependent variable: never relapsed=1, relapsed=0), univariate binary logistic regression analysis was used. Univariate variables with a *P* value of ≤0.1 were identified. To avoid multicollinearity, only one score for each performance test was chosen; for example, in the Logical Memory Test, immediate memory recall was used instead of both immediate and 30-minute delayed recall because the two are highly correlated. The remaining identified predictors were entered into a multivariate binary logistic regression model using forward selection with a *P* value of ≤0.05 indicating significance.

Among patients who completed the face-to-face interview assessments after 10 years, the outcome correlates of whether the patient relapsed over the 10 years were explored using the independent t-test for parametric continuous variables, the Chi-squared (χ^2) test for categorical variables, and the Mann-Whitney U test for non-parametric continuous variables. To handle the problem of multiple testing, the false discovery rate (FDR) (q-value) of 10% with the Benjamini-Hochberg procedure was used.

Results

Basic demographics

The study cohort was followed up for a median of 9.4 years (interquartile range, IQR 8.5-10.4) since the start of the RCT, and a median of 11.3 years (IQR 10.3-12.2) since the patient's first episode of psychosis. Of the 178 patients in the original RCT, 142 (80%) were successfully traced and interviewed, 28 (16%) declined assessment, 6 (3%) committed suicide, and 2 (1%) were unable to be contacted.

Table 1 shows the baseline (i.e., entry into the RCT) demographics and treatment characteristics during the follow-up of all patients. Forty-five percent of patients were male. They had a mean age of 24.2 years, and received education for a mean of 11.8 years. The majority of them (70%) were employed. There were no statistical baseline differences between those who relapsed and never relapsed in terms of gender, age, years of education, employment, marital status, and whether they received maintenance treatment or placebo during the randomized trial. The antipsychotics medication received over the follow-up period were similar in relapsers and non-relapsers.

[Table 1]

Relapse over the 10 years

Over the 10 years, 37 of 178 (21%) patients never relapsed following complete resolution of their positive symptoms from a first episode. In other words, relapse was observed in 141 of 178 (79%) patients, where 68 of 141 (48%) experienced one relapse, 44 of 141 (31%) experienced two relapses, 16 of 141 (11%) experienced three relapses, and the remaining 13 of 141 (9%) experienced four or more relapses. The mean number of relapse episodes was 1.5 (SD=1.4, range 0-11).

Among the 141 relapsers, the mean aggregate time spent in the first relapse was 5.4 (SD=12.6) months, and 55 (39%) of the relapsed patients required hospitalization. As for the timing of relapse, 85 of 141 (60%) patients relapsed in the first year after complete resolution of positive symptoms, 24 (17%) in the second year, 12 (6%) in the third year, 7 (5%) in the fourth year, and 4 (3%) in the fifth year.

Univariate predictors of never relapsing

Table 2 shows the univariate predictors of relapse at 10 years which had a *P* value of ≤0.1. Patients who never relapsed were less likely to be diagnosed with schizophrenia spectrum disorders, more likely to have a DUP ≤30 days, had less severe negative symptoms at baseline (especially blunted affect), had better performance in the Logical Memory (immediate and delayed recall) and Verbal Fluency Tests at baseline than those who relapsed. Other baseline predictors explored, including basic demographics, treatment received during the RCT (quetiapine or placebo), DUP, premorbid and baseline functioning, were not statistically significant in predicting relapse.

[Table 2]

To avoid the problem of multicollinearity, the single variable with the smaller *P* value in each assessment was selected for inclusion into the multivariate regression model. They included baseline diagnosis, DUP ≤30 days, SANS sum of all items, logical memory (immediate recall), and verbal fluency (correct recall).

Multivariate predictors of never relapsing

The multivariate logistic regression analysis suggested that patients who did not relapse over the 10 years were less likely to be diagnosed with schizophrenia spectrum disorders (Odds ratio, OR=0.23, 95% CI 0.13 to 0.90, *P*=0.030), more likely to have a DUP ≤30 days (OR=4.60, 95% CI 1.65 to 12.84, *P*=0.004), and performed better in the logical memory immediate recall at baseline (OR=1.10, 95% CI 1.00 to 1.22, *P*=0.050) (Table 3). The model explained 26.9% (Nagelkerke R^2) of the variance, with an overall correct classification of 81.8%.

[Table 3]

Outcome correlates of never relapsing

As shown in Table 4, more non-relapsers were married/in a stable relationship and diagnosed with non-schizophrenia spectrum disorders at 10 years. They took a lower mean dose of daily antipsychotics chlorpromazine equivalent over the follow-up period. More of them were able to stop taking antipsychotics in the 2 years prior to follow up, reported having fewer medication side effects (BARNS, UKU neurologic, and UKU others), and had a lower BMI than those who relapsed. Non-relapsers also had better social and occupational functioning at 10 years (higher SOFAS score, higher SCS score, and had more months in open employment over the 2 years prior to follow up). All these findings remained significant at a FDR rate (q value) of 10%. When the FDR rate was set to 5%, the significant variables included medication discontinuation in the past 2 years, diagnosis with schizophrenia spectrum disorders, UKU neurologic side effect, BARNS side effect, BMI, and being married/in a stable relationship.

[Table 4]

Discussion

To date, this is the first 10-year follow-up study examining the proportion and predictors of patients who did not experience psychotic relapse in the 10-year period following complete resolution of positive symptom from FEP. Our data suggested that the proportion of relapse-free patients after 10 years was 21%. This subgroup of relapse-free patients were characterized by being less likely to be diagnosed with a schizophrenia spectrum disorder, having a DUP ≤30 days, and having better short-term verbal memory following their first episode. These observed differences between relapsers and non-relapsers were unlikely to be a result of the difference in antipsychotic medications received over the ten years. Such findings not only provide an updated perspective on the characterization of patients who did not relapse after 10 years, but also expand the predictors of not relapsing to include a neurocognitive dimension. Identification of potentially modifiable predictors of not relapsing would facilitate timely intervention at the early stages of the illness, and thus produce better long-term outcome.

Relapse rates over the 10 years

Consistent with previous longitudinal studies (Shepherd et al. 1989; Linszen et al. 2001), the proportion of relapse-free patients in this study was 21%. This was slightly higher than the rate of 16.8% reported in a different 7.5-year follow-up study of FEP (Alverez-Jimenez et al. 2011). We believe the discrepancy could well be reflecting the differences in the study populations, as the previous study included FEP patients under a naturalistic setting, whereas the current study focused on FEP patients who were entirely free from any psychotic symptoms and had received maintenance treatment for at least one year under a controlled study setting. This might explain why our good prognostic first-episode cohort would have a slightly higher proportion of relapse-free patients after 10 years.

It was interesting to note that in a similar follow-up study of FEP patients who had been randomized to either dose reduction or maintenance treatment for 18 months following stabilization, the proportion of relapse-free patients at seven years was up to 35% (Wunderink et al. 2013). One reason for this higher rate of relapse-free patients in the Dutch study may be related to their use of a dose reduction arm instead of complete medication discontinuation (as in our case) during the initial clinical trial. The fact that a lower relapse rate in the initial trial was found in the Dutch study (43% in the dose reduction group; Wunderink et al. 2007) when compared to the Hong Kong study (79% in the discontinuation group; Chen et al. 2010), could explain the higher proportion of patients in the Dutch study who did not subsequently relapse in the long term.

Neurocognition and relapse

More research has begun to explore the link between neurocognitive dysfunction and relapse in psychosis, as neurocognitive function is a potentially modifiable factor. Shorter-term follow-up studies have identified baseline memory function (Verdoux et al. 2000), delayed visual reproduction (Verdoux et al. 2000), Wisconsin Card Sorting Test perseverative errors (Chen et al. 2005), Trail Making Test-B (Wolwer et al. 2008), working memory, and verbal learning (Rund et al. 2007) to be predictive of relapse in psychosis. More recently, visual working memory deterioration was found to occur preceding a psychotic relapse (Hui et al. 2016).

Here, we presented a novel finding that patients with better short-term verbal memory (immediate logical memory) at baseline were more likely to be relapse-free after 10 years. Similarly, Rund et al. (2016) have found that remitted patients who did not relapse during the first year had better neurocognitive function at 10 years than those with unstable remission or continuously psychotic during the first year, implying a link between early relapse and long-term cognitive outcome. Our data further clarified that early neurocognitive functioning is also associated with subsequent relapse status after 10 years.

DUP and relapse

DUP is an important marker for delay in first effective psychiatric treatment. The identification of DUP as a predictor is of high clinical interest due to its ability to improve clinical outcome and reduce costs, since considerable long-term studies (with follow-up durations >7.5 years) have confirmed the negative impact of a long DUP on overall symptomatic outcome (Thara & Eaton, 1996; Bottlender et al. 2003; White et al. 2009; Tang et al. 2014). In this study, the status of non-relapse at 10 years was predicted by DUP ≤30 days. This is consistent with previous short-term follow-up studies (Crow et al. 1986; Larsen et al. 2000), as well as the longer-term follow-up study of FEP (Alverez-Jimenez et al. 2011).

Given how there is no standardized method of handling the positively skewed DUP data, the adoption of the threshold value of DUP ≤30 days for categorizing subgroups made no assumption about the linear relationship between DUP and outcome. The threshold was also based on our local study, which showed that a DUP as short as 30 days is sufficient to demonstrate a significant negative impact on the remission outcome at 13 years in Chinese patients with FEP (Tang et al. 2014).

Schizophrenia spectrum disorders and relapse

Although it is widely known that a diagnosis of schizophrenia (as opposed to other psychoses) is associated with poorer outcome, the exact relationship between a diagnosis of schizophrenia and the short-term outcome of relapse remains contentious: for example, while one study found that schizophrenia patients who discontinued medication experience more relapses (Hui et al. 2013), other short-term follow-up studies have not found such a relationship (Crow et al. 1986; Lenior et al. 2005). On the other hand, the available evidence for a diagnosis of schizophrenia and the long-term outcome of relapse appears more consistent. Alverez-Jimenez et al. (2011) found

schizophrenia spectrum disorders (including schizophrenia, schizophreniform, schizoaffective, delusional, psychotic disorder not otherwise specified, and brief psychotic disorders) to be a significant univariate predictor of relapse at 7.5 years in FEP. In our 10-year study, we also found that those diagnosed at baseline with schizophrenia spectrum disorders (including schizophrenia, schizoaffective disorder, and schizophreniform disorder) were more likely to predict relapse.

Given that a non-schizophrenia diagnosis and a DUP ≤30 days were found to be significant multivariate predictors of not relapsing, one might ask if these relapse-free patients were composed of individuals diagnosed with brief psychotic disorders in the first place. Out of 37 relapse-free patients, 18 (49%) were diagnosed with schizophrenia spectrum disorders, 10 (27%) diagnosed with psychosis not otherwise specified, and the remaining 9 (24%) diagnosed with brief psychotic disorder. The postulation that relapse-free patients were simply brief psychotic disorder cases with a shorter DUP is therefore unlikely.

Limitations

Owing to the restrictive inclusion criteria used (must have complete resolution of positive symptoms, good compliance, and been on maintenance medication for at least 1 year after stabilization), the employment rate for our cohort at baseline was up to 70%. Therefore, our cohort may not have been representative of all FEP patients. Given that the cohort must have had good medication compliance to enter the study before randomization to either maintenance treatment or placebo, it is not possible to explore the effect of medication non-compliance at baseline on relapse after 10 years. However, exploratory analyses on the initially five yearly medication compliance data extracted from medical records did not predict relapse. Further, the existing medication compliance data do not allow for the differentiation between relapses that occur in patients receiving ongoing treatment and those relapsing following medication discontinuation over the ten years. A more rigorous adherence assessment to identify

the temporal relationship to the relapse events would be helpful. We did not include measures on expressed emotion and stress, which may be relevant for relapse prediction and long-term prognosis of first episode psychosis. In addition, as the prevalence of substance misuse is relatively low in the Hong Kong population, those with significant alcohol or other substance misuse in the past 3 months were excluded. Such exclusion enabled a more homogeneous sample, but leaves results incomparable to those of Western cohorts. It should also be noted that relapse in this study referred to the re-emergence or exacerbation of positive symptoms to a mild or more severe level, which may be different from the rest of the literature. Although whether patients were randomized to quetiapine/placebo during the RCT was not significantly different between relapsers and non-relapsers, we cannot entirely discard the effect of randomization on subsequent relapse after 10 years.

Clinical and research implications

The existing prediction model had 27% of the variance explained. Testable and modifiable predictors of relapse such as DUP and cognitive function would be an important addition to the long-term management of patients with psychosis and could lead to effective strategies for relapse prevention. In a study of Chinese FEP patients in Hong Kong, previous family experiences and knowledge about psychiatric illnesses were found to be important factors related to a shorter DUP (Chen et al. 2005). This is particularly relevant to our Chinese patients, because a predominant proportion of them live with their families, and the decision to seek help heavily relies on immediate family members. Early detection and psychoeducation programs could target family members to increase their awareness of signs related to onset of psychosis during the prodromal period, thereby shortening the delay to receiving timely psychiatric treatment.

The identification of neurocognitive function as marker for long-term clinical outcome such as relapse is important, because neurocognitive markers are clearly defined, relatively easy to administer, reproducible, and can objectively be measured.

There is now a growing focus in improving the outcome of psychosis by cognitive enhancement through remediation and other non-invasive approaches. More research is needed to replicate this finding before this marker is used as a screening tool for relapse in actual clinical practice.

Finally, we found that never relapsing during the 10-year period was associated with various clinical correlates, including an increased likelihood of being able to stop taking medication in the two years prior to follow-up, being married/in a stable relationship, having fewer medication side effects, and having a lower BMI. Shortening the delay to receiving timely psychiatric treatment and treatment for cognitive symptoms, especially among patients with schizophrenia spectrum disorders, thus appears to be important for improving the long-term clinical outcome of relapse.

Declaration of Interest

WGH reports having received consultation fees from Otsuka/Lundbeck, AphaSights and Eli Lilly. WTLL reports having participated as a paid consultant for Jansen. EYHC reports having received speaker honoraria from Otsuka and DSK BioPharma; received research funding from Otsuka; participated in paid advisory boards for Jansen and DSK BioPharma; received funding to attend conferences from Otsuka and DSK BioPharma. The remaining authors declare no competing interests.

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Ethical Standard

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

References

Addington D, Addington J, Maticka-Tyndale E, Joyce J (1992). Reliability and validity of a depression rating scale for schizophrenics. *Schizophrenia Research* **6**, 201-208.

Alverez-Jimenez M, Gleeson JF, Henry LP, Harrigan SM, Harris MG, Amminger GP, Killackey E, Yung AR, Herrman H, Jackson HJ, McGorry PD (2011). Prediction of a single psychotic episode: a 7.5-year, prospective study in first-episode psychosis. *Schizophrenia Research* **125**, 236-246.

Amador XF, Flaum M, Andreasen NC, Strauss DH, Yale SA, Clark SC, Gorman JM (1994). Awareness of illness in schizophrenia and schizoaffective and mood disorders. *Archives of General Psychiatry* **51**, 826-836.

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders*, 4th ed., revised. American Psychiatric Association: Washington, DC.

Andreasen NC (1983). *The scale for the assessment of negative symptoms (SANS)*. University of Iowa.

Andreasen NC (1984). *The scale for the assessment of positive symptoms (SAPS).* University of Iowa.

Barnes TR (1989). A rating scale for drug-induced akathisia. *British Journal of Psychiatry* **154**, 672-676.

Bottlender R, Sato T, Jager M, Wegener U, Wittmann J, Strauss A, Moller HJ (2003). The impact of the duration of untreated psychosis prior to first psychiatric admission on the 15-year outcome in schizophrenia. *Schizophrenia Research* **62**, 37-44.

Cannon-Spoor HE, Potkin SG, Wyatt RJ (1982). Measurement of premorbid adjustment in chronic schizophrenia. *Schizophrenia Bulletin* **8**, 470-484.

Chan SKW, So HC, Hui CLM, Chang WC, Lee EHM, Chung DWS, Tso S, Hung SF, Yip KC, Dunn E, Chen EYH (2015). 10-year outcome study of an early intervention program for psychosis compared with standard care service. *Psychological Medicine* **45**, 1181–1193.

Chen E (2004). Developing an early intervention service in Hong Kong. In *Best care in early psychosis intervention* (ed. T. Ehmann, G. W. MacEwan and W.G. Honer WG), pp.125-130. London.

Chen EYH, Dunn EL, Miao MY, Yeung WS, Wong CK, Chan WF, Chen RY, Chung KF, Tang WN (2005). The impact of family experience on the duration of untreated

psychosis (DUP) in Hong Kong. *Social Psychiatry and Psychiatric Epidemiology* **405**, 350-356.

Chen EYH, Hui CLM, Dunn EL, Miao MY, Yeung WS, Wong CK, Chan WF, Tang WN (2005). A prospective 3-year longitudinal study of cognitive predictors of relapse in first-episode schizophrenic patients. *Schizophrenia Research* **77**, 99-104.

Chen EYH, Hui CLM, Lam MML, Chiu CPY, Law CW, Chung DWS, Tso S, Pang EPF, Chan KT, Wong YC, Mo FYM, Chan KPM, Yao TJ, Hung SF, Honer WG (2010). Maintenance treatment with quetiapine versus discontinuation after one year of treatment in patients with remitted first episode psychosis: randomised controlled trial. *British Medical Journal* **341**, c4024.

Crow TJ, MacMillan JF, Johnson AL, Johnstone EC (1986). The Northwick Park Study of first episodes of schizophrenia II. A randomized controlled trial of prophylactic neuroleptic treatment. *British Journal of Psychiatry* **148**, 120-127.

Gaebel W, Riesbeck M, Wolwer W, Klimke A, Eickhoff M, von Wilmsdorff M, de Millas W, Maier W, Ruhrmann S, Falkai P, Sauer H, Schmitt A, Riedel M, Klingberh S, Moller HJ (2016). Predictors for symptom re-exacerbation after targeted stepwise drug discontinuation in first-episode schizophrenia: Results of the first-episode study within the German research network on schizophrenia. *Schizophrenia Research* **170**, 168-176.

Goldman HH, Skodol AE, Lave TR (1992). Revising axis V for DSM-IV: a review of measures of social functioning. *American Journal of Psychiatry* **149**, 1148-1156.

Guy W (1976). Abnormal involuntary movements scale (AIMS). In *The ECDEU assessment manual for psychopharmacology*, revised (ed. W. Guy), pp. 534-537. Dept of Health, Education and Welfare, National Institute of Mental Health.

Guy W (1976). Clinical global impression scale (CGI). In *ECDEU assessddment manual for psychopharmacology, revised* (ed. W. Guy), pp. 217-222. Dept of Health, Education and Welfare, National Institute of Mental Health.

Hafner H, Riecher-Rossler A, Hambrecht M, Maurer K, Meissner S, Schmidtke A, Fatkenheuer B, Loffler W, van der Heiden W (1992). IRAOS: an instrument for the assessment of onset and early course of schizophrenia. *Schizophrenia Research* **6,** 209-223.

Haro JM, Kamath SA, Ochoa S, Novick D, Rele K, Fargas A, Rodriguez MJ, Rele R, Orta J, Kharbeng A, Araya S, Gervin M, Alonso J, Mavreas V, Lavrentzou E, Liontos N, Gregor K, Jones PB, SOHO Study Group (2003).The Clinical Global Impression-Schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. *Acta Psychiatrica Scandinavica Supplementum* **416**, 16-23.

Haro JM, Novick D, Bertsch J, Karagianis J, Dossenbach M, Jones PB (2011). Cross-national clinical and functional remission rates: Worldwide Schizophrenia Outpatient Health Outcomes (W-SOHO) study. *British Journal of Psychiatry* **199**,194-201.

Hui CLM, Honer W, Lee EHM, Chang WC, Chan SKW, Chen ESM, Pang EPF, Lui SSY, Chung DWS, Yeung WS, Ng RMK, Lo WTL, Jones PB, Sham P, Chen EYH (2018). Long-term effects of discontinuation from antipsychotic maintenance following first episode schizophrenia and related disorders. *Lancet Psychiatry* **5**, 432-442.

Hui CLM, Li YK, Li AWY, Lee EHM, Chang WC, Chan SKW, Lam SY, Thornton AE, Sham P, Honer WG, Chen EYH (2016). Visual working memory deterioration preceding relapse in psychosis. *Psychological Medicine* **46**, 2435-2444.

Hui CLM, Wong GHY, Tang JYM, Chang WC, Chan SKW, Lee EHM, Lam MML, Chiu CPY, Law CW, Chung DWS, Tso S, Pang EPF, Chan KT, Wong YC, Mo FYM, Chan KPM, Hung SF, Honer WG, Chen EYH (2013). Predicting 1-year risk for relapse in patients who have discontinued or continued quetiapine after remission from first-episode psychosis. *Schizophrenia Research* **150**, 297-302.

Kay SR, Fiszbein A, Opler LA (1987). Positive and Negative Symptom Scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* **13**, 21-76.

Larsen TK, Moe LC, Vibe-Hansen L, Johannessen JO (2000). Premorbid functioning versus duration of untreated psychosis in 1 year outcome in first-episode psychosis. *Schizophrenia Research* **45**, 1-9.

Lenior ME, Dingemans PMAJ, Schene AH, Linszen DH (2005). Predictors of the early 5-year course of schizophrenia: a path analysis. *Schizophrenia Bulletin* **31**, 781-791.

Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K (1987). The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatrica Scandinavica Supplementum* **334**, 1-100.

Linszen D, Dingemans P, Lenior M (2001). Early intervention and a five year follow up in young adults with a short duration of untreated psychosis: ethical implications. *Schizophrenia Research* **51**, 55-61.

Robinson D, Woerner MG, Alvir JM, Bilder R, Goldman R, Geisler S, Koreen A, Sheitman B, Chakos M, Mayerhoff D, Lieberman JA (1999). Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Archives of General Psychiatry* **56**, 241-247.

Rund BR, Barder HE, Evensen J, Haahr U, Hegelstad WV, Joa I, Johannessen JO, Langeveld J, Larsen TK, Melle I, Opyjordsmoen S, Rossberg JI, Simonsen E, Sundet K, Vaglum P, McGlashan T, Friis S (2016). Neurocognition and Duration of Psychosis: A 10-year Follow-up of First-Episode Patients. *Schizophrenia Bulletin* **42,** 87-95.

Rund BR, Melle I, Friis S, Johannessen JO, Larsen TK, Midbøe LJ, Opjordsmoen S, Simonsen E, Vaglum P, McGlashan T (2007). The course of neurocognitive functioning in first-episode psychosis and its relation to premorbid adjustment, duration of untreated psychosis, and relapse. *Schizophrenia Research* **91**, 132-140.

Shepherd M, Watt D, Falloon I, Smeeton N (1989). The natural history of schizophrenia: a five-year follow-up study of outcome and prediction in a representative sample of schizophrenics. *Psychological Medicine Monograph Supplementary* **15**, 1-46.

Simpson GM, Angus JW (1970). A rating scale for extrapyramidal side effects. *Acta Psychiatrica Scandinavica Supplementum* **212**, 11-19.

So E, Kam I, Leung CM, Chung D, Liu Z, Fong S (2003). The Chinese-bilingual SCID-I/P project: stage 1 - reliability for mood disorders and schizophrenia. *Hong Kong Journal of Psychiatry* **13**, 7-18.

Strauss JS, Carpenter WT, Jr (1972). The Prediction of Outcome in Schizophrenia: I. Characteristics of Outcome. *Archives of General Psychiatry* **27**, 739-746.

Tang JYM, Chang WC, Hui CLM, Wong GHY, Chan SKW, Lee EHM, Yeung WS, Wong CK, Tang WN, Chan WF, Pang EPF, Tso S, Ng RMK, Hung SF, Dunn ELW, Sham PC, Chen EYH (2014). Prospective relationship between duration of untreated psychosis and 13-year clinical outcome: A first-episode psychosis study. *Schizophrenia Research* **153**, 1-8.

Thara R & Eaton WW (1996). Outcome of schizophrenia: the Madras longitudinal study. *Australian and New Zealand Journal of Psychiatry* **30**, 516-522.

Verdoux H, Lengronne J, Liraud F, Gonzales B, Assens F, Abalan F, van Os J (2000). Medication adherence in psychosis: predictors and impact on outcome. A 2-year follow-up of first-admitted subjects. *Acta Psychiatrica Scandinavica* **102**, 203-210.

White C, Stirling J, Hopkins R, Morris J, Montague L, Tantam D, Lewis S (2009). Predictors of 10-year outcome of first-episode psychosis. *Psychological Medicine* **39**, 1447-1456.

Wölwer W, Brinkmeyer J, Riesbeck M, Freimüller L, Klimke A, Wagner M, Möller HJ, Klingberg S, Gaebel W, German Study Group on First Episode Schizophrenia (2008). Neuropsychological impairments predict the clinical course in schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience* **258**, 28-34.

Wunderink L, Nieboer RM, Wiersma D, Sytema S, Nienhuis FJ (2013). Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: long-term follow-up of a 2-year randomized clinical trial. *JAMA Psychiatry* **70**, 913-920.

Wunderink L, Nienhuis FJ, Sytema S, Slooff CJ, Knegtering R, Wiersma D (2007). Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: relapse rates and functional outcome. *Journal of Clinical Psychiatry* **68**, 654-661.

Zipursky RB, Menezes NM, Streiner DL (2014). Risk of symptom recurrence with medication discontinuation in first-episode psychosis: a systematic review. *Schizophrenia Research* **152**, 408-414.

Table 1. Basic demographics and treatment characteristics for non-relapsers, relapsers, and all patients.

	Non-relapsers (n=37)	Relapsers (n=141)	All patients (n=178)	*P* value
Baseline variables				
Male; n (%)	18 (49)	62 (44)	80 (45)	0.611
Age, years; mean (SD)	23.8 (5.9)	24.3 (6.5)	24.2 (6.4)	0.685
Education, years; mean (SD)	11.4 (2.4)	12.0 (2.9)	11.8 (2.8)	0.321
Employed; n (%)	30 (81)	97 (69)	127 (71)	0.141
Married/stable;[a] n (%)	5 (14)	10 (7)	15 (9)	0.238
On placebo during the randomized trial; n (%)	17 (46)	72 (51)	89 (50)	0.579
Naturalistic antipsychotics treatment[b]				
Duration, months; mean (SD)	112.2 (11.4)	111.9 (18.5)	112.0 (17.2)	0.928
Cumulative antipsychotic dose, mg/day[c]	414.9 (259.9)	548.6 (316.2)	529.2 (311.6)	0.052

a. Data were available for 173 patients: 37 non-relapsers and 136 relapsers.

b. Antipsychotics medication received over 10 years following the start of randomized trial.

c. The mean daily dose of each antipsychotic was converted to chlorpromazine equivalent dose.

Table 2. Baseline predictors of never relapsing over the 10 years in univariate binary logistic regression analyses (P-value ≤ 0.1).

Baseline variable[a]	Non-relapsers (n=37)	Relapsers (n=141)	Univariate regression Odds ratio (95% CI)	*P* value
Diagnosed with schizophrenia spectrum disorders,[b] n (%)	18 (48.6)	109 (77.3)	0.28 (0.13-0.59)	0.001
DUP ≤30 days,[c] n (%)	14 (38)	20 (14)	3.68 (1.63-8.33)	0.002
PANSS negative symptoms	8.0 (1.4)	9.2 (3.6)	0.85 (0.71-1.01)	0.062
SANS blunting	0.4 (1.2)	2.7 (5.7)	0.78 (0.61-1.00)	0.046
SANS sum of all items	1.7 (3.2)	6.7 (14.5)	0.93 (0.86-1.00)	0.057
Logical memory immediate recall (39)	11.7 (4.5)	8.9 (4.9)	1.13 (1.03-1.24)	0.009
Logical memory delayed recall (43)	10.1 (4.9)	7.2 (5.4)	1.10 (1.02-1.19)	0.016
Verbal fluency correct recall (41)	19.9 (6.3)	17.4 (5.5)	1.08 (1.00-1.16)	0.051

CI, confidence interval; DUP, duration of untreated psychosis; PANSS, Positive and Negative Syndrome Scale; SANS, Scale for Assessment of Negative Symptoms.

a. Unless otherwise specified, values represent means (standard deviation). Number of missing observations are shown in brackets.

b. Diagnosis was categorized into schizophrenia spectrum (including schizophrenia, schizophreniform disorder, and schizoaffective disorder [=1]) and non-schizophrenia spectrum (including brief psychotic disorder and psychosis not otherwise specified [=2, reference category)).

c. DUP was classified into ≤30 days (=1) and >30 days (=2, reference category).

Table 3. Significant predictors of never relapsing over the 10 years in multivariate binary logistic regression analysis (n=137).

	B	SE	Wald	df	*P* value	Odds Ratio (95% CI)
Diagnosed with schizophrenia spectrum disorders	-1.073	0.495	4.704	1	0.030	0.34 (0.13-0.90)
DUP ≤30 days[a]	1.527	0.524	8.506	1	0.004	4.60 (1.65-12.84)
Logical memory immediate recall	0.098	0.050	3.830	1	0.050	1.10 (1.00-1.22)

CI, confidence interval; DUP, duration of untreated psychosis.

a. DUP was classified into ≤30 days (=1) and >30 days (=2, reference category).

Table 4. Outcome measures for non-relapsers, relapsers, and all patients.

Outcome variable[a]	Non-relapsers (n=30)	Relapsers (n=112)	All patients (n=142)	*P* value
Married/stable,[b] n (%)	13 (43)	23 (21)	37 (26)	0.012
Diagnosed with schizophrenia spectrum disorders, n (%)	22 (73)	107 (96)	129 (91)	<0.001
Ever alcohol use,[c] n (%)	20 (69)	62 (57)	82 (59)	0.239
Ever drug use, n (%)	3 (10)	10 (9)	13 (10)	0.859
Antipsychotics				
On clozapine	0	9 (8)	9 (6)	0.109
Antipsychotics dose during follow-up period[d]	409.1 (247.0)	571.7 (315.3)	546.1 (310.4)	0.027
Discontinue medication in the 2 years prior to follow-up	15 (50)	8 (7)	23 (16)	<0.001
Medication compliance[e]	3.3 (0.6)	3.6 (0.5)	3.5 (0.5)	0.072
Attitude towards medication[f]	3.3 (0.6)	3.3 (0.6)	3.3 (0.6)	0.682
PANSS				
Positive	7.5 (1.9)	8.2 (2.9)	8.0 (2.7)	0.098
Negative	7.7 (1.3)	8.1 (2.1)	8.0 (2.0)	0.261
General psychopathology	18.5 (3.5)	19.1 (3.8)	19.0 (3.8)	0.398
CDSS[g]	1.1 (2.6)	1.0 (2.5)	1.0 (2.5)	0.938
SAS[h]	0	0.009 (0.1)	0.008 (0.1)	0.636
AIMS[i]	0	0.2 (1.2)	0.2 (1.0)	0.421
BARNS[j]	0	0.4 (1.2)	0.3 (1.1)	0.003
UKU[k]				
Psychic	1.7 (2.3)	2.0 (2.5)	2.0 (2.5)	0.622
Neurologic	0.1 (0.2)	0.5 (1.2)	0.5 (1.1)	0.001
Autonomic	0.3 (0.6)	0.6 (1.2)	0.6 (1.1)	0.089
Others	0.3 (0.8)	0.9 (1.2)	0.8 (1.2)	0.021
BMI[l]	23.9 (5.3)	26.9 (5.1)	26.1 (5.4)	0.007
SOFAS past 1 month	66.4 (9.1)	62.0 (9.1)	63.0 (9.3)	0.019
Strauss & Carpenter Scale[m]	3.5 (5.1)	3.2 (0.6)	3.3 (0.6)	0.022
Months in open employment in recent 24 months[n]	20.4 (7.3)	16.5 (9.1)	17.3 (8.9)	0.020

PANSS, Positive and Negative Syndrome Scale; CDSS, Calgary Depression Scale for Schizophrenia; SAS, Simpson-Angus Scale; AIMS, Abnormal Involuntary Movement Scale; BARNS, Barnes Akathisia Rating Scale; UKU, Udvalg for Kliniske Undersøgelser; BMI, Body Mass Index; SOFAS, Social and Occupational Functioning Assessment Scale.

a. Unless otherwise specified, values represent means (standard deviation). Fishers exact test was used for cells that have count less than 5.

b. Data were available in patients who had an end-of-follow-up assessment: 30 non-relapsers, 111 relapsers, and 141 patients overall.

c. Schizophrenia spectrum disorders (schizophrenia, schizophreniform disorder, schizoaffective disorder) vs. non-schizophrenia spectrum (including psychosis not otherwise specified, brief psychotic disorder, delusional disorder).

d. The mean daily dose of each antipsychotic was converted to a chlorpromazine equivalent dose. Data

were available in patients who had an end-of-follow-up assessment: 21, 112, and 133 patients.
e. Medication compliance was measured using the modified Adherence Rating Scale. Higher scores indicate better adherence behavior. Data were available in patients who had an end-of-follow-up assessment: 20, 94, and 114 patients.
f. Medication attitude was measured using the modified Adherence Rating Scale. Higher scores indicate a more positive attitude. Data were available in patients who had an end-of-follow-up assessment: 22, 94, and 116 patients.
g. Data were available in patients who had an end-of-follow-up assessment: 30, 111, and 141 patients.
h. Data were available in patients who had an end-of-follow-up assessment: 24, 106, and 130 patients.
i. Data were available in patients who had an end-of-follow-up assessment: 24, 105, and 129 patients.
j. Data were available in patients who had an end-of-follow-up assessment: 24, 105, and 129 patients.
k. Data were available in patients who had an end-of-follow-up assessment: 17, 102, and 119 patients.
l. BMI is the weight in kilograms divided by the square of the height in meters. Data were available in patients who had an end-of-follow-up assessment: 28, 103, and 131.
m. Data were available in patients who had an end-of-follow-up assessment: 30, 106, and 136 patients.
n. Data were available in patients who had an end-of-follow-up assessment: 28, 107, and 135 patients.