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Review

Are we getting any better at staying better? The long view on relapse and recovery in first episode nonaffective psychosis and schizophrenia

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***Abstract*:** Relapse in, and recovery from, schizophrenia has been acknowledged since the disease was first described. In this review the authors summarize the long-term (>100 years) data on relapse and recovery in schizophrenia by reviewing the extant older and modern relevant literature. The authors systematically question the utility of pharmacological and nonpharmacological interventions, with an emphasis on first episode nonaffective psychosis. The method used is a narrative review of earlier meta-analytic and systematic reviews.

Antipsychotic medication discontinuation studies suggest a role for prophylactic maintenance treatment in the majority of people with schizophrenia, despite recent debate on this subject. The authors conclude that long-term outcomes, including relapse and recovery rates, have improved in the last 100 years, though prospectively identifying those people who do not require long-term antipsychotic treatment has not yet been possible. Data also suggests that interventions and outcomes during the first 5 years of the disease can influence the long-term schizophrenia trajectory.

Keywords: psychosis, psychosocial interventions, recovery, relapse, schizophrenia

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Introduction

Relapse of schizophrenia and nonaffective psychosis has been linked to poor treatment response, and people experiencing multiple psychotic relapses also appear to have more functional deterioration.[1] Furthermore, these individuals who have a relapsing course of illness are less likely to marry or sustain long relationships. Dutta and colleagues have shown that repeated relapse is also linked to an increased risk of suicidal behaviour,[2] and a systematic review noted younger previously high functioning men were particularly at risk of suicide.[3]

Factors affecting recovery from psychosis have been highlighted in recent years, and social disruption, job loss and increased stigma are also indirect consequences of relapse. These factors have been difficult to measure in research studies but are clearly important when examining recovery from psychosis.

Here, we review relapse and recovery after first episode non-affective psychosis and established schizophrenia, taking a 'long view' of the relevant literature spanning over 100 years. We examine definitions of relapse and recovery and unpick their relationship to each other, in the pre- and post-antipsychotic eras. The role of antipsychotics and non-pharmacological interventions are also reviewed, with a focus on relapse.

The authors used a nonsystematic narrative review, however, they have placed emphasis on and summarized the accepted hierarchy of evidence including: systematic reviews, meta-analyses and relevant high-quality studies

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(randomized controlled trials [RCTs] and observational studies).

Definitions of relapse and recovery

A systematic review identified that most studies or guidelines (62% of 87) used hospitalization as a sufficient proxy marker for relapse.[4] Modern health systems (especially those with community home treatment or crisis teams), however, can mean that a marked deterioration in symptoms and functioning may not always be accompanied by hospital admission. Similarly, other factors including suicide attempt, violence and social reasons can lead to hospital admission when there has not been a clear relapse in terms of functioning or symptoms. Burns and colleagues in a Delphi study involving an expert panel, noted that three criteria (for relapse) should be measured including: psychopathology, readmission to hospital and social functioning.[5]

The current method used to define relapse appears to be to first ascertain if remission has been achieved, as defined by the Schizophrenia Working Group.[6] This states that patients will have experienced:

> an improvement in core signs and symptoms to an extent that any remaining symptoms are of such low intensity that they no longer interfere significantly with behaviour and are below the threshold typically utilized in justifying an initial diagnosis of schizophrenia.

Duration of the improvement was stipulated to be at least 6 months, and symptom intensity was suggested to be measured using rating scales, such as the Positive and Negative Symptom Scale (PANSS) rating of mild, $\leqslant 3$, or the Brief Psychiatric Rating Scale (BPRS) $\leqslant 3$. Acknowledging that some people do not experience remission, Eisner and colleagues gave examples from earlier literature that characterized 'type1' and 'type 2' categories of relapse. 'Type 1' referred to people who experienced re-emergence of positive symptoms, and 'type 2' involved an exacerbation of symptoms that had previously stabilized.[7]

With regard to symptom reoccurrence, unlike treatment resistance (where clear criteria have been set),[8] there is no consensus as to a symptom threshold required for relapse, one large trial set multidimensional criteria, including any of the following: rehospitalization/need for care, increase of 25% in PANSS total from baseline when the baseline was greater than 40 and various measures of clinically significant deterioration.[9]

Given the lack of consensus definition, the authors have opted for a broad definition of relapse in this review, including when symptom exacerbation occurs alone, and when it impairs an individual's functioning, as well as including literature using hospitalization in the definition.

Recovery

The concept of recovery from schizophrenia, involving social and occupational recovery rather than a simple amelioration of symptoms, has been highlighted in recent years[10] As above, definitions of recovery vary, using clinical symptoms and psychosocial functioning as well as recommendations of multidimensional measurement including duration of recovery (e.g. 2 years[11,12]).

Conceptually these definitions are separate from the 'recovery model,' which identifies that regardless of psychiatric symptoms, people with mental illness pursue personal goals, engage in valued social roles and abide in a community of their own choosing. This reflects an emphasis on the challenges for people with schizophrenia other than symptoms, including limited social support, unemployment, loneliness and stigma. The 'recovery model' places emphasis on self-management, peer-led interventions and shared decision-making regarding treatment, including pharmacological treatment.[10]

From these definitions it is clear that relapse and recovery are separate concepts, and this review examines both of these concepts in the pre- and post-antipsychotic medication eras.

Relapse and recovery from the pre-antipsychotic era to the present day

Kraepelin,[13] in 1919 instilled an influential therapeutic pessimism as he believed 'dementia praecox' or schizophrenia would inevitably deteriorate, whilst he thought the course in bipolar psychosis was fluctuant, though benign. However, Kraepelin's own series of hospital-based cases revealed spontaneous complete recovery in approximately 15% of his dementia praecox patients, although data on relapse in this series appears lacking.

An important meta-analysis by Hegarty and colleagues,[14] which included 25 early (1895–1925) cohort studies, found that 27.6% of patients with Kraepelinian dementia praecox had a good social outcome, with no improvement in this rate occurring over those 30 years. Follow up of the cohorts was limited to less than 10 years. This time period was chosen as it preceded both antipsychotic medication and electroconvulsive therapy. The larger meta-analysis covered studies up to the 20th century, and whilst methodological factors make assessing the role of treatments on recovery difficult, antipsychotic medication had the largest beneficial effect, regardless of diagnostic definition (narrow or broad), though nonspecific interventions also had an impact, for example, for the Kraepelinian construct 31% of patients improved with antipsychotics compared with 22.5% with nonspecific interventions.

Reporting similar findings to the Hegarty meta-analysis, the Iowa 500 study of 200 people with narrowly defined schizophrenia assessed between 1934 and 1944, found that only 34% of those followed up ($n = 186$) could be discharged into the community following their first hospitalization.[15]

Interpretation of these follow-up studies is difficult due to the use of different diagnostic criteria and markers of outcome. In a careful review of the literature, McKenna[16] identified two other methodologically rigorous studies from the pre-antipsychotic era: Langfeld's study of 100 patients followed up for 7–10 years,[17] and a similar study of 160 patients followed up for 6–8 years.[18] Both found a similar proportion of people, approximately 20%, were in the best two outcome groups, with most experiencing complete recovery.

The authors are unaware of studies that measured both relapse and recovery solely in the pre-antipsychotic era. The best example from this period is Manfred Bleuler's follow-up study of 208 people with schizophrenia, admitted to a single hospital site between 1942 and 1943[19] (68 being first admissions to hospital). All patients were followed up until 1963 or 1965, or until their death. Antipsychotic treatment in this cohort was intermittent, that is, no prophylactic use. Bleuler divided illness trajectory according to simple, undulating and atypical courses, with a comment on end state (recovered, mild/moderate and severe), onset (acute/chronic), constituting eight classes. Three classes were undulating, representing those with recovery (22%), moderate/mild end stage (27%) and severe end stage (9%). The stage of illness was based on symptomatic and functional outcomes. When reassessing this dataset using modern criteria such as the Diagnostic and Statistical Manual (DSM), results worsened to 12% (recovered), 25% (moderate/mild) and 11% (severe). Cases of schizoaffective disorder accounted for most of these outcome differences.

Morgan and colleagues[20] compared these results with a 10-year follow up of the AESOP cohort, and two other studies, a Swiss follow-up study by Ciompi and colleagues[21] and the International Study of Schizophrenia (ISoS).[22] The authors excluded the Ciompi study, because the diagnostic criteria were unclear, and only 289 of 1642 cases were reported. Morgan and colleagues found that in their sample of 126 people with nonaffective psychosis, 15% of people had an undulating course with a good outcome (recovery), and 35% an insidious onset and undulating course with a good outcome. Respective percentages for people with schizophrenia in the ISoS cohort were 29% and 23% for these two good prognostic categories.

Therefore, in a cohort of those treated without maintenance medication (Bleuler's cohort), 12% of people had a relapsing/remitting diagnosis of schizophrenia and a good outcome, compared with approximately 50% of those who may have received antipsychotic medication between episodes, in the modern era.

Studies examining long term recovery and remission

A systematic review[12] examined recovery in 50 studies of people with established schizophrenia using clinical and social domains as well as the duration of recovery for at least 2 years.[12] This found a 13.5% recovery rate (or good outcome). There was no relationship between recovery and gender, duration of follow up, origin or quality of the study and first episode status. In addition, there was no suggestion that recovery rates were improving over time, despite possible improvements in service delivery or treatment.

Similar values for complete recovery were found in Warner's analysis of 114 follow-up studies between 1904 and 2000. Warner found that between 11 and 13% of people with a diagnosis of schizophrenia recovered completely, with 22–53% experiencing social recovery.[11]

Lally and colleagues[23] examined remission and recovery after FEP, including affective psychoses. They concluded that 7 years after initial onset the pooled remission rate was 58% and recovery rate was 38%, they also observed that recovery rates had not improved over recent years.

The Morgan and colleagues 10-year follow up of the AESOP FEP cohort (see above) noted heterogeneity in the long term outcome studies, including 13 studies conducted since 1980, with a minimum of 8 years follow up. This was exemplified by variation in remission rates, from 20% to 78%, dependent on the differing definitions used. Only three of these studies were conducted in first episode samples.[20]

It should be noted that a recent review of remission criteria use over the last 10 years indicates that milder symptoms predict a longer time in remission, suggesting that a treatment goal should be minimal symptoms.[24] Scales for measuring functional benefits of clinical remission include the Functional Remission of General Schizophrenia scale.[24]

Studies in people with untreated psychosis

A limited number of long term follow-up studies of people with untreated schizophrenia exist in the post-antipsychotic era. Conducting such a randomized trial would certainly be unethical, although some observational studies exist where people with schizophrenia have either not received antipsychotic medication at all or have only taken it for a short period of time. Interpretation of such studies is difficult, due to selection bias.

The most methodologically rigorous (defined catchment area, defined diagnostic criteria and examination) involved the assessment of a cohort of 510 people from China. Some people received antipsychotic treatment, and some did not (never treated/remaining untreated). After 14 years of follow up, rates of remission were 16.4% in the never treated/remaining untreated group compared with 34.1% in the treated group.[25] Other outcomes were also poorer for this untreated group, including mortality and social functioning. It should be noted that the mean age of the never treated group was 48.2 years, indicating that a proportion of people who may have presented at a younger age and experienced remission may not have been picked up. A study[26] conducted in an urban area of India sampled a younger population of 75 people with never treated schizophrenia (mean age of 36) and found that they were more symptomatic and severely disabled than the comparator group of 75 people whose illness had been treated.

A follow-up catchment area study[27] in Ethiopia conducted monthly follow ups (over a mean 3.4 years) of 321 people with schizophrenia, 89.6% of whom were treatment naïve. The study noted that approximately one-third of patients were continuously unwell, with most of the rest having an episodic course. Only 5.7% were in complete remission throughout the follow-up period. In the last year of follow up, 27.4% were in complete remission in the month prior to assessment.

Related studies have included that of Harrow and colleagues[28] who followed up a cohort of people with their first or second admission to hospital with schizophrenia. Of the 70 people, 7 of 14 (50%) untreated patients recovered, compared with 15% of treated patients. As highlighted by Leucht and Davis,[29] this small selected cohort was predominantly affluent, drawn mainly from those admitted to a psychoanalytic-based hospital, and may well have not required antipsychotic medication due to good function.

Other related work includes two follow-up studies of early intervention cohorts, from the AESOP and OPUS trials. In the former, 10-year later data of a FEP cohort of 557 people from Nottingham and South East London revealed that 46% of people with FEP were not prescribed antipsychotic medication in the 2 years prior to the 10-year follow-up assessment, and were in remission.[20] The attrition rate was low, with 85% of people being followed up, although it is unclear what proportion of the 46% fulfilled diagnostic criteria for schizophrenia.

A similar follow-up of the Danish OPUS trial identified 61% of the original 496 people with schizophrenia[30] spectrum disorder, of whom 30% had no psychotic symptoms and were not taking antipsychotics. Unfortunately, the high attrition rate and selection bias in this follow up, makes interpretation difficult.

A 2018 national cohort study[31] used 'within same individual' statistics to retrospectively follow up people admitted in Finland with a first episode of schizophrenia, over a maximum 20-year period (although the average duration was shorter).

They found discontinuing the antipsychotic medication or not taking antipsychotic medication was associated with 'treatment failure' which was an unusual composite of rehospitalization and death. Limitations of this large observational study include an inability to impute causality.

Stage of illness and recovery

The greatest variability in the schizophrenia illness trajectory appears to be in the initial stages. In an evaluation of first admission studies over a mean follow-up time of 17.4 years, 54% of patients exhibited social recovery despite 32% showing poor clinical outcomes (data adapted from Ram and colleagues[32]). Therefore, whilst clinical and social morbidity can go hand in hand, a significant proportion of patients, often women, will demonstrate social recovery despite ongoing symptoms.

The importance of the early course of illness is also reflected in 15- and 25-year illness trajectories, the Harrison and colleagues international study[22] determined that the course of illness during the first 2 years was the strongest predictor of 15-year outcomes. Notably, 16% of early unremitting cases achieved late phase recovery (similar to Bleuler's cohort). The authors concluded that sociocultural conditions appear to modify long-term illness course and that early intervention may produce long-term gains.

A careful study of Bleuler's cohort (described above[19]) reveals that, on the whole, the first 5 years of illness onset appeared to be a critical period, and no further deterioration was seen in the cohort with the 5-year outcome, which was roughly equivalent to 20-year outcome.

The role of antipsychotic medication in relapse prevention

To the best of the authors' knowledge there currently are no known demographic or clinical variables that reliably predict relapse.[33]

As reviewed above, antipsychotic medication appears to have beneficial effects in terms of recovery in a significant number of people.

Studies examining the role of prophylactic antipsychotic medication in preventing relapse have relied mainly on discontinuation studies, using placebo and observational study design, dating back to the 1980s. These studies predominantly followed up people who have experienced symptomatic remission from their first episode of psychosis.

Zipursky and colleagues[34] systematically reviewed symptomatic relapse subsequent to nonaffective FEP after medication discontinuation, finding a first-year relapse rate of 77% (based on six studies) with 2-year recurrence of over 90%. By contrast, the 1-year relapse rate for those individuals still taking medication was 3%.

The largest meta-analytic review of relapse and antipsychotic medication remains that of Leucht and colleagues[35] which examined relapse (defined as hospital admission) between 7 and 12 months from 65 different trials. They found active medication was associated with a 27% relapse rate compared with 64% for placebo after 1 year, with a number needed to treat (NNT) for benefit = 3, and NNT is defined as the number of people taking prophylactic medication to prevent relapse, compared with controls. This represents a major effect compared with other active treatments in clinical medicine. They also found an improved quality of life and fewer aggressive acts whilst taking antipsychotic medication, but also more weight gain, sedation and movement disorders compared with placebo.

The same meta-analysis also showed long acting injectable (depot) medication reduced relapse rates more than oral medication (relative risk of 0.31 *versus* 0.46). This latter finding is important, as almost all trials of oral antipsychotic do not measure antipsychotic levels (which are a recognized measure of adherence or concordance[36]). This was addressed in first episode illness in an independent RCT that compared relapse rate in people with recent onset schizophrenia whose illness had been treated briefly with oral risperidone. Those consenting were randomized to remain on oral risperidone or to switch to long acting injectable risperidone. After 1 year of follow up they found long-acting injectable risperidone reduced the relative risk of relapse (compared with active treatment, oral risperidone) by a surprising 84.7%. Cognitive remediation and healthy behaviour training did not affect the outcome.[37]

In a related analysis which acknowledged the problems inherent in a dichotomized definition of relapse, Takeuchi and colleagues[38] meta-analysed 11 antipsychotic trials in which people with

schizophrenia were randomized to maintenance treatment or placebo. They found that continued antipsychotic treatment over a 1-year period was associated with continued symptom improvement, compared with placebo.

Alvarez-Jimenez and O'Donohoe and colleagues,[39] in their systematic review of FEP discontinuation studies, adopted broad inclusion criteria, identifying seven trials, with varying relapse definitions (symptom reoccurrence and multidimensional) with follow up between 1 and 7 years. There was a wide variation in relapse rates. In the medication continuation groups, relapse varied between 0% and 68%, whereas 19–89% relapsed in the medication discontinuation group. It should be noted that Boonstra and colleagues.[40] had to stop their trial early due to a significant deterioration in the discontinuation group, with 88% being relapse free in the continuation group, and 82% having relapse of illness in the discontinuation group after 9 months (relapse defined on basis of symptoms).

Most discontinuation studies are short term (up to 2 years), and other study designs are required to assess relapse rates over the longer term. These consist of observational studies of discontinuation trials, early intervention trials and case register studies.

The Wunderink and colleagues[41] study reignited interest in relapse and antipsychotics, being a 7-year follow up of an earlier 2-year discontinuation first episode trial. It cast doubt on the long-term benefits of antipsychotic medication. They examined long-term symptomatic relapse in people originally enrolled in an antipsychotic dose reduction/withdrawal and maintenance trial. Their findings at 2-year follow up of those discontinuing antipsychotic medication were similar to the rest of the literature (increased symptomatic relapse, 43% *versus* 21%), though at 7-year follow up they found no significant difference in relapse rates (61.5% *versus* 68.6%). Furthermore, they found improved psychosocial functioning in those originally assigned to the dose reduction/withdrawal group. There was no statistically significant difference in antipsychotic dose between groups (2.2 mg haloperidol equivalent dose reduction *versus* 3.6 mg in the maintenance treatment group), and both groups had spent equivalent time off antipsychotic medication. Symptoms were assessed in the 2 years prior to 7-year follow up (it was essentially an uncontrolled study during years 2–7). It should also be noted that the groups at inclusion were not matched for diagnosis, and more people with schizophrenia were in the maintenance group, with nonblinded assessors of the outcome. Therefore, interpretation of the level of functioning and the role of antipsychotics needs to be cautious, as pointed out by Correll and others.[42] Nevertheless, despite increased relapse in the discontinuation group, outcomes were not any worse in this group.

A 10-year follow up of a quetiapine discontinuation study[43] in remitted first episode nonaffective psychosis studied 178 people who took part in the original trial. No difference in psychosocial functioning between those originally assigned to antipsychotic withdrawal (placebo) was found, but after 10 years 39% of the placebo (discontinuation) group and 21% of those who had up to an extra year of quetiapine had a poor outcome (defined as persistent psychosis, need for clozapine and suicide), which was significant (risk ratio = 1.84). Relapse rate during the original study mediated this outcome. A short length of initial treatment and dichotomized outcome have been put forward as valid critiques of this trial. However, irrespective of these factors, the group who received placebo and had more initial relapses did not show improved psychosocial functioning, as found by Wunderink and colleagues[42]

Do antipsychotics cause relapse?

The high rates of early relapse in a number of studies led some to query whether a discontinuation/rebound syndrome was causing relapse *via*, for example, dopamine supersensitivity.[44] This theory originated in the 1970s and postulates that upregulation of dopamine receptors by antipsychotics causes a super sensitivity psychosis upon antipsychotic discontinuation, which could explain relapse. Arguments for this are based on the observation of increased D_2 density in post mortem and positron emission tomography (PET) studies of people treated with antipsychotic medication, compared with PET findings in antipsychotic-naïve individuals.[45]

Furthermore, preclinical studies have found increased locomotor activity following discontinuation of antipsychotics, suggesting alterations of the dopamine system. This could possibly explain relapse within the first year or so following antipsychotic discontinuation, though preclinical data in psychotic illness remains difficult to interpret,

given the lack of clear animal models of psychotic illness. It should also be noted that no clear pathophysiology has emerged for relapse, though there appears to be a state component to dopamine synthesis capacity in psychotic illness,[46] and antipsychotics do not appear to alter this.[47]

Arguments against this include the observation that relapse can occur with partial agonists (which have fewer effects preclinically, though these are still present), that relapse rates are similar to abrupt and gradual discontinuation,[29] and that discontinuation of depot risperidone in a large cohort of people did not result in autonomic dysfunction or changes in prolactin, suggesting a withdrawal syndrome characterized by physical symptoms was unlikely.[48] Although, both clozapine and quetiapine bind to D_2 receptors, they have less affinity than other antipsychotics, though discontinuation of them is associated with longer-term relapse of psychotic illness.

Nonpharmacological interventions, relapse and recovery

Recovery

Nonpharmacological interventions have been less extensively studied than pharmacological interventions. A 2013 review[49] used meta-analyses and randomized controlled trials to identify pertinent interventions, which included assertive community treatment, cognitive behavioural therapy (CBT), cognitive remediation, family psychoeducation, illness self-management, social skills training and supported employment. CBT has the most extensive evidence base of all nonpharmacological interventions, with a recent meta-analysis suggesting a small effect on functioning at the end of trials that became nonsignificant on follow up.[50] Evidence from well-conducted studies suggests no benefits for CBT in preventing relapse.[51]

There are over 40 RCTs of cognitive remediation in schizophrenia, and a 2011 meta-analysis found a moderate effect size for verbal episodic memory in 23 studies,[52] though 2 recent methodologically rigorous trials have failed to show any clear effects on neuropsychological tests or functioning,[53] or primary outcome measures of executive function and memory.[54] A Cochrane review of 53 studies of family intervention showed it may decrease relapse frequency (relative risk = 0.55, NNT = 7), with the authors noting some negative studies may have been missed.[55]

Illness self-management is based on psychoeducation, behavioural tailoring of medication into one's daily routine, relapse prevention and coping strategies. The evidence is difficult to interpret owing to RCTs taking place in different countries, though they have found improvement in community functioning compared with treatment as usual (TAU[49]) Older meta-analyses of social skills training suggest a moderate effect size for assertiveness, and social functioning, though a 2017 analysis suggested no clear benefits on these measures when risk of bias was accounted for.[56]

A review of supported employment found individual support and placement programmes had the strongest evidence on nonvocational outcomes in schizophrenia, for example, quality of life.[57]

Newer psychosocial treatments may also have the potential to improve recovery, with evidence from retrospective studies suggesting adjunctive approaches such as social cognitive therapy may provide more benefit, though large RCTs would be necessary to test this fully.[58]

Early intervention services. Alvarez-Jimenez and colleagues[59] identified three studies, with rehospitalization and their own criteria as markers of relapse, and concluded that early intervention services (EIS) were superior to TAU (odds ratio = 1.8; NNT = 8). Bird and colleagues[60] reviewed four trials and found EIS decreased the risk of relapse (35% compared with 52%; odds ratio = 1.47). A recent meta-analysis[61] drew similar conclusions, with (RR, 0.71; NNT, 10.0) from seven trials, with follow-up data up to 24 months. It is perhaps worth noting that the three largest trials: OPUS, OPUS II and RAISE found no difference in either clinical symptoms, hospitalization, or remission status in later years.

CBT. The same review[59] also found no benefit for CBT after combining three studies of individual CBT (including one study of cannabis focused CBT) *versus* various interventions including supportive counselling (active control) and TAU. Bird and colleagues concluded that there was insufficient evidence to recommend the use of CBT for relapse prevention in FEP.

Mixed interventions. Gleeson and colleagues[62] studied 7 months individual CBT and family interventions *versus* EIS alone and found an advantage for these interventions in terms of relapse at 1 year but this was not sustained at 30 months, with a deterioration in the experimen-

tal group. No differences were noted when medication status was added to the model.

Family therapy. Alvarez-Jimenez and colleagues[59] examined two trials of family therapy (FT) on relapse prevention, as defined by hospital admission, both *versus* TAU. One found a decrease in hospital admissions at 18 months but the second study showed no advantage for FT. Bird and colleagues[60] included one FT study, an older trial of fluphenazine medication at two doses, plus or minus 'crisis-oriented' FT. This study found fewer relapses in those receiving higher doses of fluphenazine with FT compared with those receiving higher doses of fluphenazine alone, although study numbers were small and it was unclear whether the intervention really was FT.

Taken together, these findings on psychosocial interventions in FEP suggest that early intervention services do appear to have a role in relapse prevention, at least in the short term. The effectiveness of CBT and family interventions in relapse prevention, however, is unclear so far. Nevertheless, the absence of positive supportive data for psychosocial interventions does not imply they have no value in promoting autonomy, hope and self-esteem, all of which can be hard to capture in trial design.

Conclusion

Schizophrenia is clearly a relapsing and remitting condition for the majority of people, and relapse itself can impair prognosis. Nevertheless, it seems that Kraepelin was overly pessimistic as many individuals with acute psychosis, approximately 20%, fully recover and never experience relapse subsequently, even in the absence of antipsychotic medication.

Analysis of the 'long view' data indicates that long-term outcomes in schizophrenia and psychosis, including relapse and recovery rates, appear to have improved over the last 100 years. In the authors' opinion, the main factors affecting this modest improvement appear to be the use of (low-dose) antipsychotic medication, community-based service delivery models including EIP and arguably some diminution in the stigma associated with schizophrenia.

Examination of older cohort studies and more recent work suggests antipsychotics are effective in promoting relapse prevention and overall outcome. The single largest distinction between antipsychotics appears to be formulation rather than a brand that is, long-acting injectable versus orals. This reflects the main issue in chronic disease management, namely (lack of) medication adherence or concordance. Nevertheless, the debate will continue about the long-term role of antipsychotics, in view of their adverse side effects and the associated stigma around psychosis.

To the best of the authors' knowledge, as yet, there is no reliable prognostic method to determine who will require long-term maintenance medication, and who will not, after a first episode.

Future treatment directions will include prospective studies of FEP samples, with an emphasis on personalizing treatment, perhaps through possible biomarkers, to predict who will and who will not benefit from longer-term antipsychotic prophylaxis. Future research should be carried out with the objective of confirming the suggestions that sustained treatment early in the illness (in the first 5 years) could ameliorate long-term illness trajectory and recovery.

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