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Psychosis relapse during long-acting injectable antipsychotic treatment: An individual participant data meta-analysis of 19 trials and 5,111 individuals with schizophrenia-spectrum disorders

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Abstract:	Background: Most individuals with schizophrenia-spectrum disorders experience relapses, which increases the risk of morbidity and mortality. Since non-adherence with antipsychotic maintenance treatment may affect up to half of individuals, psychosis relapse can often be confounded by unnoticed treatment interruption. Research of relapse during confirmed antipsychotic exposure has basic clinical and neurobiological implications, yet data are limited. Methods: Systematic review and individual participant data meta-analysis (IPDMA) of clinical trials of long-acting injectable antipsychotics (LAIs) for psychosis relapse-prevention, following IPD-PRISMA guidelines. Datasets were identified by searching relevant repositories up to August/01/2019. Each LAI arm was re-analyzed as a separate cohort, further identifying sub-cohorts of individuals with and without prospectively determined symptom remission (PSR). Pooled incidence rates, incidence rate ratios (IRRs) and hazard ratios (HRs) were derived from within-cohort Poisson, Kaplan-Meyer and Cox regression analyses. Outcomes: Nineteen treatment cohorts (n=5,111), of which 2,938 had PSR, while 2,173 did not (non-PSR), with 3,959·53 actual observed participant years were meta-analyzed. Pooled incidence of relapse was 22·97 per 100 patient-years, being 14·76 per 100 patient-years for the PSR sub-cohort and 31·51 per 100 patient-years for the non-PSR sub-cohort (IRR=0·39, 95%CI=0.29-0·53). The strongest predictors of relapse were having tardive dyskinesia (HR=2·39, 95%CI=1·05-5·42) and comorbid substance use disorder (HR=1·55, 95%CI=1·15-2·10) at treatment onset. Predictors were similar between the PSR and non-PSR sub-cohorts, except for greater impact of substance use disorder in PSR (p<0·01). Interpretation: A sizeable proportion of individuals with schizophrenia-spectrum disorders relapses during confirmed antipsychotic treatment. This risk doubles in individuals not achieving symptom remission, but even in remitted patients, 1 out of 7 patients relapsed in <1 year. Developing tardive dyskinesia and comorbid substance use may have pathophysiological implications for relapse on confirmed antipsychotic treatment.

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Psychosis relapse during long-acting injectable antipsychotic treatment: An individual participant data meta-analysis of 19 trials and 5,111 individuals with schizophrenia-spectrum disorders

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Conflict of Interest:
Dr Rubio has been a consultant or has received speaker honoraria from: Lundbeck, Teva. He has also received royalties from UpToDate, and grant support from Alkermes. Dr Tiihonen reports personal fees from the Finnish Medicines Agency (Fimea), European Medicines Agency (EMA), Eli Lilly, Janssen-Cilag, Lundbeck, and Otsuka; is a member of advisory board for Lundbeck, and has received grants from the Stanley Foundation and Sigrid Jusélius Foundation. Dr Taipale reports personal fees from Janssen-Cilag. Dr. Tiihonen and Dr. Taipale have participated in research projects funded by grants from Janssen-Cilag and Eli Lilly to their employing institution. Dr Malhotra has served as a consultant for Forum Pharmaceuticals and has served on a scientific advisory board for Genomind, Inc. Dr. Correll has been a consultant and/or advisor to or has received honoraria from: Acadia, Alkermes, Allergan, Angelini, Axsome, Gedeon Richter, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, MedAvante-ProPhase, Medscape, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Sumitomo Dainippon, Sunovion, Supernus, Takeda, and Teva. He has provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, Rovi, Supernus, and Teva. He received royalties from UpToDate and grant support from Janssen and Takeda. He is also a stock option holder of LB Pharma. Dr Kane has been a consultant and/or advisor for or has received honoraria from Alkermes, Allergan , LB Pharmaceuticals, H. Lundbeck, Intracellular Therapies, Janssen Pharmaceuticals, Johnson and Johnson, Merck, Minerva, Neurocrine, Newron, Otsuka, Pierre Fabre, Reviva, Roche, Sumitomo Dainippon, Sunovion, Takeda, Teva and UpToDate and is a shareholder in LB

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Abstract:
Background: Most individuals with schizophrenia-spectrum disorders experience relapses, which increases the risk of morbidity and mortality. Since non-adherence with antipsychotic maintenance treatment may affect up to half of individuals, psychosis relapse can often be confounded by unnoticed treatment interruption. Research of relapse during confirmed antipsychotic exposure has basic clinical and neurobiological implications, yet data are limited.

Methods: Systematic review and individual participant data meta-analysis (IPDMA) of clinical trials of long-acting injectable antipsychotics (LAIs) for psychosis relapse-prevention, following IPD-PRISMA guidelines. Datasets were identified by searching relevant repositories up to August/01/2019. Each LAI arm was re-analyzed as a separate cohort, further identifying sub-cohorts of individuals with and without prospectively determined symptom remission (PSR). Pooled incidence rates, incidence rate ratios (IRRs) and hazard ratios (HRs) were derived from within-cohort Poisson, Kaplan-Meyer and Cox regression analyses.

Outcomes: Nineteen treatment cohorts (n=5,111), of which 2,938 had PSR, while 2,173 did not (non-PSR), with 3,959·53 actual observed participant years were meta-analyzed. Pooled incidence of relapse was 22·97 per 100 patient-years, being 14·76 per 100 patient-years for the PSR sub-cohort and 31·51 per 100 patient-years for the non-PSR sub-cohort (IRR=0·39, 95%CI=0.29-0·53). The strongest predictors of relapse were having tardive dyskinesia (HR=2·39, 95%CI=1·05-5·42) and comorbid substance use disorder (HR=1·55, 95%CI=1·15-2·10) at treatment onset. Predictors were similar between the PSR and non-PSR sub-cohorts, except for greater impact of substance use disorder in PSR ($p<0·01$).

Interpretation: A sizeable proportion of individuals with schizophrenia-spectrum disorders relapses during confirmed antipsychotic treatment. This risk doubles in individuals not achieving symptom remission, but even in remitted patients, 1 out of 7 patients relapsed in <1 year. Developing tardive dyskinesia and comorbid substance use may have pathophysiological implications for relapse on confirmed antipsychotic treatment.

Funding: Northwell Health funded the study yet did not influence the approach.

Key words: predictors, epidemiology, non-adherence, confounder, long-acting injectable antipsychotic, schizophrenia, relapse

Putting research into context:

Evidence before this study:

The vast majority of individuals with a schizophrenia-spectrum disorder will have several relapses over their course of illness. The mechanisms involved in psychosis relapse, other than treatment non-adherence, are not well understood. In fact, since more than half of individuals with schizophrenia are treatment non-adherent at some point, and since there are no effective routine methods to quantify adherence, it is often impossible to disentangle relapse despite ongoing treatment from relapse because of treatment interruption. This distinction is critical to identify causal mechanisms of psychosis relapse. We have proposed to study relapse during treatment with long-acting injectable antipsychotics, since continuous exposure to treatment can be confirmed by injection dates. Using this approach, previous research from national registries has found that up to one third of individuals are re-hospitalized despite assured treatment exposure. However, lack of data on symptom severity in national registries prevents from concluding that such large proportion of individuals would relapse even after having demonstrated treatment adequate response.

Added value of this study:

Using precise participant-level inclusion criteria and a harmonized analytic approach across datasets, this study generated reliable estimates of the risk of relapse during assured antipsychotic exposure, as well as its predictors. These results confirm that psychosis relapse during ongoing treatment is relatively common, even in individuals who previously demonstrate symptom remission. Particularly, these data suggest a causal association between sensitivity to chronic dopaminergic blockade by antipsychotic drugs manifested by tardive dyskinesia, and subsequent psychosis relapse.

Implications of all the available evidence:

Antipsychotic drugs are highly efficacious in treating acute psychosis and preventing relapse compared with no treatment, yet a sizeable proportion of individuals may relapse over time, despite ongoing antipsychotic treatment. Future research should investigate the role of dynamic changes in the dopaminergic system in relapse during antipsychotic treatment.

INTRODUCTION

Schizophrenia-spectrum disorders are characterized by recurrent relapses for most individuals.[1] Relapse acutely impacts occupational and social functioning, may endanger the patient and others, and often requires inpatient hospitalization, increasing healthcare costs.[1] Despite accounting for much of the personal and societal burden of schizophrenia-spectrum disorders, the mechanisms of relapse are insufficiently understood.[2]

Arguably, the largest risk factor for relapse in schizophrenia-spectrum disorders is non-adherence with antipsychotic maintenance medication.[3] Unfortunately, non-adherence may be present in >50% of patients with schizophrenia-spectrum disorders at any time, although methods to measure antipsychotic adherence in routine care are generally unreliable.[3] Therefore, it is often uncertain whether relapse occurs with or without antipsychotic exposure, being a common confounder in clinical practice and research. To remove the confounder of covert non-adherence, we have proposed to study relapse in individuals treated with long-acting injectable antipsychotics (LAIs), for whom exposure to antipsychotic drugs is continuous, given the long-acting nature of these formulations, and can be confirmed by simple documentation of LAI administration.[4]

To our knowledge, the first study to explicitly measure the incidence of relapse during assured antipsychotic exposure was a re-analysis of a one year-long relapse-prevention clinical trial with risperidone-LAI, which reported a relapse rate of 18·3%.[5] Although informative, this finding was based on a relatively small sample of 323 individuals, and factors, such as minimum time to achieve therapeutic plasma level before counting relapse, were not considered. In another clinical sample of 99 individuals with a first psychotic episode treated with LAI, and followed for a mean of 20 months, the incidence of relapse using operationalized criteria was 21·2%.[6] More recently, in a large study of a cohort of individuals with schizophrenia-spectrum disorders from the Finnish national registry who were continuously treated with LAIs for up to two decades, the rate of re-hospitalization for psychosis was 31·5% corresponding to 12·0 events per 100 patient-years.[7] These data revealed that relapse despite ongoing treatment was more prevalent than previously expected, although the lack of symptom severity data in national registries precluded confirming that these individuals had responded to treatment prior to relapse.

The confounder of antipsychotic non-adherence also applies to the study of the risk factors of relapse. For example, recent analyses demonstrated that at least 20-36% of the risk of cannabis use on relapse was mediated through declared non-adherence.[8] Given the challenges in the identification of non-adherence using routine methods, this figure is likely an underestimate, and theoretically this confounding effect is true of many risk factors for relapse. Therefore, the direct effects of risk factors of psychosis relapse in schizophrenia-spectrum disorders cannot be easily disentangled from the effects mediated through treatment non-adherence. This distinction is critical to identify what factors have direct neurobiological effects on worsening psychotic symptoms despite ongoing treatment. Some studies have examined predictors adjusting for treatment adherence,[9] yet this approach is limited by the inability to quantify it accurately using routine methods.[3] Other studies have measured risk factors removing the confounder of non-adherence yet with relatively small samples or insufficient characterization of covariates.[5–7] A reliable quantification of the risk factors of psychosis relapse that minimizes confounding is critical to inform research on the pathophysiology of relapse, and ultimately guide precision medicine for effective relapse-prevention.

Since most of the existing data on the risk of relapse in schizophrenia are exposed to the confounder of treatment non-adherence, and those that have addressed this issue by studying individuals continuously treated with LAIs are limited by small sample sizes or insufficient symptom severity data, reliable data on this basic aspect of the course of illness is necessary. We will leverage the increasing amount of available participant-level data from relapse-prevention LAI trials to conduct a participant-level meta-analysis (IPDMA) to measure the incidence and predictors of psychosis relapse without the confounder of non-adherence. This resource-intensive approach involves direct control of the data, allowing more thorough and appropriate analyses than aggregate-data meta-analyses. By harmonizing inclusion criteria, covariate

definitions and statistical analysis, this approach produces more reliable and transparent results, and is considered the "gold standard" method to summarize data from systematic reviews.[10,11]

METHODS

This IPDMA was conducted following the PRISMA-IPD guidelines.[11] The protocol for the conduct of this study was registered on 07/18/2019 in the PROSPERO International prospective register of systematic reviews (2019 CRD42019137439; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019137439). We followed a two-stage IPD meta-analysis approach,[12] in which we first re-analyzed individual cohorts of individuals treated with LAIs (i.e., treatment arms allocated to LAIs from relapse-prevention clinical trials) using a comparable approach, and then pooled the results from the re-analysis of each cohort using a random effects meta-analysis. A two-stage IPD meta-analysis was chosen as logistically it was unfeasible to place all of the individual participant data within a unique analytic platform, and because the two-stage approach has shown to produce similar results as the single stage method.[12]

Data search and access:

We conducted a systematic search in search engines pubmed.gov and clinicaltrials.gov, and in the individual participant clinical trial data repositories yoda.yale.edu, clinicalstudydatarequest.com and data-archive.nimh.nih.gov, using the query "psychosis AND antipsychotic AND injectable AND randomized" as of up to 8/1/2019. Identification of eligible datasets was conducted independently by 2 researchers (JR, DG) by abstract/study protocol, and disagreements were resolved by consensus. Eligibility criteria were: 1) Participants diagnosed with a schizophrenia-spectrum disorder (schizophrenia, schizophreniform disorder, schizoaffective disorder, psychosis not otherwise specified), 2) Clinical trial with ≥ 1 treatment arm assigned to an LAI, 3) Follow-up ≥6 months, 4) Analyzable data for relapse. Once potentially eligible studies were identified, we contacted the study sponsors directly to request access to the original de-identified data if the data were not hosted in data repositories. For data hosted in repositories, those were contacted directly, requesting the eligible datasets. Access to the de-identified data was achieved following the signing of data transfer agreements between each data host (YODA, CSDR, Otsuka, NDCT) and the investigators. Data hosts were able to review this manuscript prior to submission for publication, but did not have any role in the study design or execution, or the decision to publish the data.

Individual cohort re-analysis:

Each treatment arm allocated to an LAI in each dataset (i.e., relapse-prevention clinical trial) was treated as a separate cohort, which was analyzed using standardized procedures. The full code in R[13] used to re-analyze each cohort was written and double checked by two investigators independently for accuracy (JR, GS) (Suppl Text 1). Analyses were conducted in the secure analytic environment maintained by the host if data were not transferred directly to the investigators. The first analytic step consisted in the identification of individuals who were exposed to the LAI for sufficient time to achieve a therapeutic plasma level according to minimal treatment periods determined by the investigators based on the minimal therapeutic plasma level defined by the AGNP[14] and the time to achieve that plasma level shown in the pharmacodynamic curves for each LAI. This period depended on the dose and LAI, and is specified in the study protocol, ranging overall between 1-4 weeks. Individuals exposed for a minimum time to develop a therapeutic antipsychotic blood level were identified and constituted the total cohort, from which we identified the two subgroups of individuals who did or did not achieve symptom remission (i.e., prospective symptom remission (PSR) cohort, defined as mild or less in all of the positive symptom subscales of the Positive and Negative Symptom Scale (PANSS) or the items "conceptual disorganization", "hallucinations", "unusual thought content", and "suspiciousness" in the Brief Psychiatric Rating Scale (BPRS) for two consecutive assessments (for NCT01136772 and NCT00330863 only one assessment was used due to lack of consistent consecutive data). Once the total cohort of exposed individuals and the PSR and non-PSR cohorts were established, we identified for each subject whether study-defined relapse criteria were met, and the time to event or censoring. Only LAI treatment periods were included in the analyses, and if individuals were allocated to placebo, they were censored at that point in time. These data were entered into a Kaplan-Meier model using the R package 'survival', which generated time to relapse and incidence rate for relapse measured in events per 100 participant-

years, separately for the total cohort and the PSR and non-PSR cohorts. Next, we calculated the values for baseline covariates for the total cohort and the PSR and non-PSR cohorts, following the standard definitions listed in Suppl Table 1. For each cohort, distribution of covariates was examined, and those with skewed distribution were categorized. Then, these covariates were entered into a Cox proportional hazards model, from which we derived Hazard Ratios (HRs) and 95% Confidence Intervals (95%CIs). Therefore, from each cohort we obtained descriptive statistics of the outcome and covariates, HRs (95%CIs) for covariates available in each dataset, and survival rates per week. In addition, we calculated the interaction terms between sub-cohort status (i.e., PSR versus non-PSR) and each baseline covariate to measure differences in the associations between covariates and symptom remission status. Finally, two authors (JR, GS) conducted a risk of bias assessment for each individual cohort using the "Newcastle-Ottawa Scale for assessing the quality of non-randomized studies[15]" (Suppl Table 3). This risk of bias tool was deemed adequate since although several datasets had been randomized, data were analyzed as an arm-based clinical cohort, rather than as a randomized study. Each series of steps was iterated for each cohort.

Meta-analysis:

The results from the re-analysis of each cohort (descriptive statistics of covariates, survival analyses and Cox regression analyses) were exported from the analytic environment hosted by each sponsor to a common environment manage by the study investigators to conduct the second stage of the meta-analysis. We used the package 'metafor' and 'meta' to pool: 1) Descriptive data of baseline covariates using a random effects model, which generated the combined dataset of patient characteristics, 2) Incidence rate across cohorts to generate the combined incidence rate of relapse measured in events per 100 participant-years observed, and 3) HRs obtained from the Cox regression in each cohort to generate pooled HRs and 95%CIs for baseline covariates on time to relapse (since HRs are not distributed symmetrically around 1, they were log transformed for the meta-analysis and once pooled the log transformation was reverted). These steps were conducted separately for the data derived from the total cohort and data derived from the PSR and non-PSR sub-cohorts. We quantified differences between each sub-cohort in: 1) Descriptive data of the baseline covariates, 2) Incidence rate of relapse and 3) Association between covariates and time to relapse using a random effect meta-analyses of within-study derived risk difference for categorical covariates and mean difference for continuous covariates, incidence rate ratio, and interaction terms of subgroup by covariate, using a significance threshold of p Value <0·05.

Heterogeneity for the incidence rate was measured with the I^2 statistic (with >50% indicating significant heterogeneity) as well as tau (τ), which refers to the estimated standard deviation of underlying true effects across studies.[16] The risk of publication bias was measured with the visual inspection of the funnel plot and the Duval and Tweedie fill and trim test.[17] Furthermore, to measure the heterogeneity in the incidence rate introduced by methodological differences between cohorts, we conducted additional sensitivity analyses for: 1) Percentage of cohort from the US, 2) Patient status upon referral (acute vs stable), 3) Outcome definition, 4) Dataset sponsor, and 5) Risk of bias score, estimating for each of these covariates the percentage of the variance of heterogeneity explained.

Ethics of research:

Each data owner obtained ethics committee approval prior to sharing the de-identified data.

Role of the funding source:

Neither Northwell Health as the institution funding this study, nor the data hosts had any role in study design, data collection, data analysis, data interpretation, or writing of and decision to publish the manuscript. The corresponding author had full access to all data and had final responsibility for the decision to submit the manuscript for publication. The code to analyze the data is available in the supplementary material.

RESULTS

Characteristics of included cohorts

The systematic search resulted in 19 treatment cohorts of individuals continuously exposed to LAIs for sufficient time to achieve a therapeutic plasma level (Suppl Figure 1). These corresponded to 5,111 individuals in the total cohort with 3,959·53 actual observed participant years, and 2,938 individuals in

the PSR cohort remission with 2,369·65 actual observed participant-years, and 2,173 individuals in the non-PSR cohort with 1551·39 actual observed participant-years. Twelve of the 19 treatment cohorts had maximum observation periods >1 year, 10 included only stable patients, and 14 used standardized relapse criteria. The completion rate ranged between 30·76% and 93·80%, only one included individuals with a first episode psychosis, and three were sponsored by academia and not industry (Table 1). Risk of bias was deemed rather low for most of the cohorts, with a mean Newcastle-Ottawa Scale score for all included cohorts of 4·37 out of a maximum (lowest risk of bias) of 6 (Suppl Table 2). The pooled characteristics of the total cohort and of the PSR and non-PSR sub-cohorts are summarized in Table 2. There was a significantly greater proportion of individuals in the US, smoking, and with tardive dyskinesia (TD), akathisia and extrapyramidal symptoms (EPS) in the non-PSR than in the PSR sub-cohort, and symptom severity, BMI and illness duration were greater in the non-PRS subgroup, who were also older and had worse functioning (Table 2).

Pooled risk of relapse

Among the individuals included in the meta-analysis, there was a pooled incidence rate of study-defined relapse of 22·97 events per 100 participant-years (Figure 1a). Among PSR individuals, the incidence rate of relapse was 14·76 events per 100 participant-years (Figure 1b), versus 36·51 events per 100 participant-years for non-PSR individuals (Figure 1c). The IRR of relapse comparing PSR vs non-PRS individuals was 0·39 (95%CI=0.29-0·53). In the meta-regression analyses, between-study heterogeneity was significantly introduced by proportion of cohort from the US (β=0·01, R^2=23·58%, p=0·005), study sponsor (β=-0·77, R^2=26·87%, p=0·011), and study quality measured by the Newcastle-Ottawa Score (β=-0·43, R^2=11·19%, p=0·009) (Suppl Figure 2). There was no risk of publication bias observed according to the Duval and Tweedie trim and fill test, with zero studies missing on the left side, p<0·01 (Suppl Figure 3). Incidence of study-defined relapse during follow-up for the total cohort and the PSR as well as non-PSR sub-cohorts are displayed in Figure 2.

Risk factors of relapse

For the total cohort, relapse risk was significantly associated with moderate or worse TD at baseline (HR=2·39, 95%CI=1·05-5·42), substance use disorder (HR=1·55, 95%CI=1·15-2·10), proportion of cohort from the US (HR=1·55, 95%CI=1·27-1·90), baseline CGI score (HR=1·28, 95%CI=1·12-1·48), nicotine smoking (HR=1·20, 95%CI=1·02-1·40), male sex (HR=1·19, 95%CI=1·02-1·39), and positive symptom severity at baseline (HR=1·04, 95%CI=1·02-1·06). Decreased risk of relapse was associated with older age at diagnosis (HR=0·97, 95%CI=0·96-0·99). The only significant difference in association of baseline risk factors and time to relapse between PSR and non-PRS individuals was for substance use disorder, whose association in PRS individuals (HR=2·36, 95%CI=1·39-4·01) was significantly greater versus non-PRS individuals (HR=1·36, 95%CI=1·34-1·39) (p<0·01) (Table 3).

DISCUSSION

Using precise participant-level inclusion criteria, (e.g., minimum time post-injection to assure therapeutic antipsychotic plasma levels, prospective demonstration of symptom remission), as well as a harmonized analytic approach across datasets, this IPDMA generated reliable estimates of the risk of relapse during assured antipsychotic exposure, as well as its predictors. Results indicate that, overall, more than one in five individuals relapsed over an average of about nine months. While the relapse risk was close to one in three individuals with non-PRS, still as many as one in seven individuals with PRS relapsed over the observation period of <1 year during confirmed antipsychotic treatment, confirming that this phenomenon is not merely the result of treatment resistance or recurrence of symptoms after inadequate stabilization. Furthermore, the predictor analyses corroborated the association of various factors in increasing the risk of relapse beyond the risk resulting from treatment non-adherence, including TD and substance use disorder, supporting a potentially causal association with relapse.

We observed a relatively large variation in the incidence rates of relapse between cohorts, which was partly related to methodological differences in study design between datasets. Percentage of individuals in the US, academic sponsorship, and greater risk of bias were correlated with a greater incidence rate of psychotic relapse and explained a meaningful proportion of the variance in heterogeneity. Conversely, including patients with acute psychosis and structured vs investigator defined outcome did not

significantly influence the incidence of relapse. Individuals treated in the US may have been more prone to meet relapse criteria due to less availability of environmental support (e.g., family support, access to psychotherapy, etc) compared to other countries.[18] Also, industry sponsorship has been found to be associated with more favorable outcomes in clinical trials, probably resulting from a composite of factors (e.g., large sample size, multiple centers and countries, recruitment in professional centers, enrollment of less severely ill patients), which may result in lower relapse rates.[19]

The observed overall incidence rate of psychotic relapse of 23 events per 100 patient years in the entire cohort, and especially the relapse rate of 15 events per 100 patient years for individuals with PSR, for whom history of treatment responsiveness was confirmed prospectively, were greater than the 12 events per 100 patient years observed in a national cohort in Finland during LAI treatment over a cumulative 20-year period.[7] The lower incidence rate found in the Finnish national registry may have to do with the limited sensitivity of re-hospitalization for psychosis as measure of relapse, compared to the gold standard operationalized criteria used by most trials included in this study.[20] Also, since risk of relapse decreases over time, the Finnish national registry study may have found lower incidence rates since it observed individuals for a somewhat longer period of time. Furthermore, incidence appeared to decrease with age, and being the Finnish cohort older, lower incidence ratee would have been expected too. It is important to note that although LAIs assure antipsychotic exposure while being used, these drugs are very often discontinued too. Claims studies suggest that only a small minority of individuals stay on continuous LAI treatment without interruption for longer than 6 months.[21,22] Therefore, it very well may be possible that individuals, especially in naturalistic settings, often discontinue treatment before allowing it time to fail, again decreasing the apparent incidence of relapse during continuous treatment. Taking into account these considerations, the results of this study confirm the findings of the Finnish national registry, in which about one in three individuals on continuous treatment experienced relapse in long-term follow-up, highlighting that relapse despite ongoing antipsychotic treatment is relatively common. Furthermore, our results prove that this is not only the result of treatment resistance or symptom recurrence after insufficient stabilization, since even after confirming prospectively symptom remission, the incidence rate was still larger than in the Finnish national registry.

Importantly, although for the most part baseline symptom severity did not inform relapse risk, the degree of "antipsychotic responsiveness" (manifested by achieving symptom remission) did, and should be considered an important prognostic predictor. This finding reinforces the notion that LAIs should be used to rule out treatment resistance,[23] and that residual symptoms despite treatment should prompt the consideration of clozapine given the high incidence of clinical worsening in these individuals.

Various baseline predictors point towards potential areas to focus the next steps in the neurobiological research of psychosis relapse. Tardive dyskinesia was strongly associated with relapse. The pathophysiology of TD likely results from chronic blockade of dopamine D2 receptor in the striatum by antipsychotic drugs,[24] and the only approved drugs for the treatment of TD are VMAT2 inhibitors,[25] which prevent presynaptic release of striatal dopamine.[26] Furthermore, animal models suggest that upon chronic exposure to antipsychotics, increments in the density and affinity of dopaminergic receptors in the striatum may mediate "breakthrough psychosis".[27] Altogether, these findings suggests that a differential response in dopaminergic striatal circuits may be relevant for a greater likelihood of relapse in a subgroup of vulnerable patients. Aberrant striatal functioning has been consistently observed in antipsychotic drug response compared with non-response in first episode psychosis individuals,[28,29] and the results from this study encourage the extension of that work to relapse risk in patients with chronic psychosis. Since some individuals were antipsychotic-free at baseline, it is not possible to judge the role of other motor side effects of antipsychotics that do not persist after the treatment is withdrawn, such as akathisia or acute parkinsonism, and while the HR was above 1 for both of these antipsychotic adverse effects, they did not reach statistical significance. Nevertheless, developing akathisia or acute parkinsonism have been associated with worse antipsychotic response,[30–32] and these data suggests that this may be at least partly mediated by neurobiological mechanisms rather than only by greater non-adherence rates among individuals who develop these side effects. Since motor effects of antipsychotic drugs are thought to

involve the effects of these drugs on striatal dopaminergic receptors,[33,34] future research should confirm an interaction in striatal functioning between antipsychotic and motor effects of antipsychotic drugs. Similarly, the strong association between substance use disorder at baseline and significantly greater risk of relapse suggests a pathophysiological overlap between neurobiological underpinnings of addiction or direct physiological effects of drugs and relapse risk in psychosis, independent of non-adherence. The fact that comorbid substance use disorder seems to have been associated with psychosis in the context of likely dopaminergic blockade by antipsychotic drugs, this can lead to various hypotheses. One hypothesis would be that comorbid substance use may have de-stabilized individuals vulnerable to experience psychotic symptoms through non-dopaminergic mechanisms. However, even psychotomimetic non-dopaminergic agents have been reported to have some effect on the dopaminergic system.[35] An alternative hypothesis would be that chronic antipsychotic exposure may have resulted in aberrant regulation of the dopaminergic system, making it more vulnerable to the known effects of various drugs of abuse on the dopaminergic system.[29,35–37] Unfortunately, the clinical neuroscience research on individuals with primary schizophrenia-spectrum disorders and comorbid substance use disorders has been very limited, despite over 20% of individuals with psychosis meeting criteria for a comorbid substance use disorder.[38] More research in this area is greatly necessary.

Another neurobiological implication of these results is that "treatment responsiveness" may be a dynamic phenotype over the course of illness, as we found that individuals with previous symptom remission may experience recurrence of psychosis despite continued exposure to the treatment to which they responded in the first place. These findings align with previous reports of decreased effect sizes of antipsychotic drugs in second compared to first psychotic episodes.[39] A large body of clinical neuroscience research has been developed using "treatment responsiveness" as a clinical phenotype, especially in first episode psychosis research, with the implication that it can reflect differences in the neurobiology of psychosis.[28] These results invite to test the hypothesis that a change in "treatment responsiveness" is associated with yet to be elucidated neurobiological changes.

The IPD meta-analysis had several advantages over traditional study-level meta-analyses, and in fact this work would not have been possible using an aggregate data meta-analysis approach. Since individual participant modeling was possible, this allowed maximizing the representativeness of the cohort to the population of interest (i.e., individuals with meaningful antipsychotic plasma levels), and comparability of the outcome of interest and of covariates. Additionally, the IPD approach allowed for a meta-analysis of within-study associations, which is much more accurate than a meta-regression analysis of between study associations, as the within-study approach removes ecological bias introduced by differences in study characteristics.[11] Finally, this approach allowed for more transparent and reproducible research, as the code to generate and analyze the cohorts was provided (Suppl Text 1). The movement towards data sharing is critical for transparency and reproducibility, and also makes it possible to address questions that may require large sample sizes. We found that industry sponsored datasets were more often available for re-analyses than academy sponsored studies. Initiatives such as that of the NIMH to encourage sharing of individual patient data in the NIMH Data Archive are extremely necessary to close the gap in open data access in academia-sponsored research.

This work should be interpreted in the context of several potential limitations. First, the observation periods were at the most 2 years for each cohort, therefore incidence of relapse after this period was not measured. Second, most of these patients were derived from industry-sponsored trials, which may recruit less complex and severely ill patients than treated under "real world" conditions. The meta-regression analyses confirmed that industry-sponsored studies had lower incidence rates compared to academic-sponsored trials, which could have resulted in our effects being an under-estimate. Third, studies varied in their attrition rates, with completion rates ranging between 39·42% and 93·38%, which could have resulted in a relevant underestimation of the incidence of relapse. Fourth, five out of 19 cohorts used non-standardized relapse criteria (i.e., investigator decision), however the meta-regression analyses did not show that this had any effect on the incidence rates of relapse in these cohorts.

In summary, this work demonstrates that the course of illness during assured continuous antipsychotic exposure in schizophrenia may be characterized by relapses in a sizeable proportion of cases, even after

symptom remission is achieved, suggesting that "treatment responsiveness" may be dynamic for some individuals with a psychosis-spectrum diagnosis. Furthermore, motor side effects of antipsychotic treatment, especially TD, which expresses a differential pattern of adaptation of the dopaminergic system to chronic D2 blockade, and comorbid substance use disorders, may be critically involved in the mechanism of relapse. Future efforts should use these findings to inform neurobiological research on the pathophysiology of relapse in psychosis and the identification of prognostic biomarkers.

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Table 1·Dataset characteristics

Dataset	Total cohort (n)	Remission subgroup (n;%)	No remission subgroup (n;%)	LAI exposure (Months)	Patient status at entry in survival model*	Relapse definition criteria⏀	Completer rate (%)★	Year	Primary diagnosis ǂ	Sponsor	Risk of bias (6=least risk)
NCT00111189	852	512 ; 60·10%	340; 39·90%	12 to 24	Acutely ill allowed	Csernansky criteria	39·42	2009	SCZ	Industry	4
NCT00210717-R	353	106 ; 30·01%	247; 69·97%	12 to 24	Acutely ill allowed	Investigator determined	63·00	2007	SCZ	Industry	3
NCT00210717-P	378	136 ; 35·98%	242; 64·02%	12 to 24	Acutely ill allowed	Investigator determined	59·92	2007	SCZ	Industry	3
NCT00119756-50	81	40 ; 49·38%	41; 50·62%	6 to 12	Stable at entry	Investigator determined	81·16	2006	SCZ	Industry	4
NCT00119756-75	83	45 ; 54·21%	38; 45·79%	6 to 12	Stable at entry	Investigator determined	76·92	2006	SCZ	Industry	4
NCT00119756-100	86	47 ; 54·65%	39; 45·35%	6 to 12	Stable at entry	Investigator determined	81·81	2006	SCZ	Industry	4
NCT01529515	469	213 ; 45·42%	256; 54·48%	>=24	Acutely ill allowed	Csernansky criteria	69·51	2014	SCZ	Industry	4
NCT00216580	46	21 ; 45·65%	25; 54·35%	>=24	Acute only	Csernansky criteria	83·72	2007	FEP	Industry	6
NCT01193153	638	186 ; 29·15%	452; 70·85%	12 to 24	Acute only	Csernansky criteria	30·76	2013	SCA	Industry	4
NCT00216476	338	193 ; 57·10%	145; 42·90%	>=24	Stable at entry	Csernansky criteria	64·15	2007	SCZ+SCA	Industry	5
NCT01136772-P	145	53 ; 36·55%	92; 64·45%	>=24	Acutely ill allowed	Csernansky criteria	40·47	2014	SCZ+SCA	Academia	4
NCT01136772-H	143	52 ; 36·36%	91; 64·64%	>=24	Acutely ill allowed	Csernansky criteria	42·69	2014	SCZ+SCA	Academia	4
NCT00330863	119	30 ; 25·21%	89; 74·10%	>=24	Acutely ill allowed	Csernansky criteria	70·93	2011	SCZ+SCA	Academia	4
NCT00320489	247	171 ; 69·23%	0 ; 30·77%	>=24	Stable at entry	Csernansky criteria	58·70	2010	SCZ	Industry	5
NCT00088491-1	140	140 ; 100%	0 ; 0%	6 to 12	Stabilized for 4-8 weeks	Csernansky criteria	93·38	2006	SCZ	Industry	5
NCT00088491-2	141	141 ; 100%	0 ; 0%	6 to 12	Stabilized for 4-8 weeks	Csernansky criteria	84·44	2006	SCZ	Industry	5
NCT00088491-3	318	318 ; 100%	0 ; 0%	6 to 12	Stabilized for 4-8 weeks	Csernansky criteria	90·00	2006	SCZ	Industry	5
NCT00705783	269	269 ; 100%	0 ; 0%	12 to 24	Stabilized for 4-12 weeks	Csernansky criteria	49·17	2013	SCZ	Industry	5
NCT00706654	265	265; 100%	0 ; 0%	6 to 12	Stabilized for 4-6 weeks	Csernansky criteria	80·65	2013	SCZ	Industry	5

Legend: *"Acutely ill allowed" does not exclude that stable patients were entered into the model, whereas "Acutely ill only" does. "Stable at entry" refers to recruiting subjects meeting only study-defined stability criteria, whereas "Stabilized" refers to patients going through an oral phase stabilization and only those meeting study-defined stability criteria were included in the model. Study-defined stability may differ from our remission criteria (2 consecutive visits with mild or less in psychotic items of BPRS/PANSS) therefore explaining the gap in the remission subgroup in studies recruiting subjects stable at entry.

ǂ SCZ: Schizophrenia, FEP: First episode psychosis, SCA: Schizoaffective.

⏀ For investigator determined recommendation by sponsor was >20% worsening in total psychopathology score; Csernansky criteria based on any of the following: 1) Psychiatric hospitalization, 2) Increase in the level of psychiatric care (e·g·, from clinic visits to day treatment), 3) Increase of 25 percent from base line in the total score on the Positive and Negative Syndrome Scale, 20 or an increase of 10 points if the base-line score was 40 or less (total possible scores range from 30 to 210, with higher scores indicating greater severity of symptoms), 4) Deliberate self-injury; suicidal or homicidal ideation that was clinically significant in the investigator's judgment, 5) Violent behavior resulting in clinically significant injury to another person or property damage, 6) Substantial clinical deterioration, defined as a change score of 6 ("much worse") or 7 ("very much worse") on the Clinical Global Impressions Scale (possible scores range from 1 to 7, with a score of 4 indicating no change, 1 to 3 improvement, and 5 to 7 worsening).

★Proportion of individuals who could have completed the trial (i.e., no event, no placebo) who did complete the trial (%).

Table 2· Pooled baseline characteristics in total cohort and subgroups of total cohort by prospective symptom remission

	Total cohort (n=5,111)				Cohort with prospective symptom remission (n=2,938)				Cohort without prospective symptom remission (n=2,173)				p Value comparing both sub-cohorts*
Baseline Characteristic	**k**	**n with data**	**n with condition**	**%**	**k**	**n with data**	**n with condition**	**%**	**k**	**n with data**	**n with condition**	**%**	
Male	19	5,111	3115	60·95	19	2,938	1,777	60·48	14	2,173	1340	61·67	0·11
US	19	5,111	2185	42·75	19	2,938	1,269	43·19	14	2,173	916	42·15	**< 0·01**
Family history	4	937	251	26·79	4	792	205	25·88	1	145	46	31·72	0·82
Nicotine smoking	15	4,193	2424	57·81	15	2,190	1,145	52·28	12	2,073	1279	63·95	**0·02**
Substance use disorder	4	1,045	326	31·20	4	321	81	25·23	4	740	245	33·98	0·68
>=3 hospitalizations	9	2,443	1033	42·28	9	1,610	718	44·60	6	849	300	35·34	0·21
Hospitalized in previous year	11	2,798	984	35·17	11	1,686	681	40·39	8	1,128	304	26·95	0·43
At least moderate TD	17	4,577	45	0·98	17	2,404	16	0·67	14	2,173	97	4·46	**< 0·01**
At least moderate akathisia	17	4,577	90	1·97	17	2,404	38	1·58	14	2,173	151	6·95	**< 0·01**
At least moderate EPS	17	4,577	405	8·85	17	2,404	194	8·07	14	2,173	251	11·55	**0·02**
	k	**n with data**	**Mean**	**SD**	**k**	**n with data**	**Mean**	**SD**	**k**	**n with data**	**Mean**	**SD**	
Age	19	5,111	39·92	0·91	19	2,938	39·75	0·89	14	2,173	40·08	1·28	0·31
BMI	19	5,111	27·73	0·48	19	2,938	27·38	0·47	14	2,173	28·12	0·64	**0·03**
Age at diagnosis	17	4,004	26·06	0·47	17	2,539	26·41	0·50	12	1,484	25·40	0·64	**< 0·01**
Duration of illness	17	4,004	13·90	1·07	17	2,539	13·17	1·01	12	1,484	14·07	1·63	**< 0·01**
CGI-S	19	5,111	3·70	0·12	19	2,938	3·49	0·12	14	2,173	4·14	0·09	**< 0·01**
PANSS Total	18	4,992	67·80	2·73	18	2,908	64·35	2·60	13	2,087	75·38	2·96	**< 0·01**
PANSS General	18	4,992	33·29	1·27	18	2,908	31·96	1·21	13	2,087	36·42	1·49	**< 0·01**
PANSS Positive	18	4,992	15·85	0·92	18	2,908	14·27	0·91	13	2,087	19·13	0·85	**< 0·01**
PANSS Negative	18	4,992	18·63	0·65	18	2,908	18·03	0·59	13	2,087	19·79	0·80	**< 0·01**
Personal and social performance scale	6	3,028	57·00	3·92	6	1,175	60·66	3·99	6	1,682	54·10	3·03	**< 0·01**

Legend: k= Number of datasets for which data was available; n= Number of individual participants; SD=Standard Deviation; US=United States; TD=Tardive dyskinesia; EPS=Extrapyramidal symptoms; BMI=Body Mass Index; CGI=Clinical Global Impressions Severity score; PANSS=Positive And Negative Syndrome Scale. * Significant results at $p < 0.05$ are in bold

Table 3· Pooled within-study associations between baseline covariates and time to relapse

	TOTAL COHORT (n=5,111)				COHORT WITH PROSPECTIVE SYMPTOM REMISSION (n=2,404)				COHORT WITHOUT PROSPECTIVE SYMPTOM REMISSION (n=2,173)				p Value comparing both sub-cohorts
Moderator Variables	**Hazard Ratio**	**Lower limit 95% CI**	**Upper limit 95% CI**	**Hetero-geneity (I^2%)**	**Hazard Ratio**	**Lower limit 95% CI**	**Upper limit 95% CI**	**Hetero-geneity (I^2%)**	**Hazard Ratio**	**Lower limit 95% CI**	**Upper limit 95% CI**	**Hetero-geneity (I^2%)**	
Male sex	**1·19**	**1·02**	**1·39**	**0·00**	1·27	0·93	1·72	20·79	**1.58**	**1.32**	**1.90**	**87.18**	0.05
Age	0·99	0·98	1·00	39·38	0·99	0·98	1·00	19·59	**1.02**	**1.01**	**1.02**	**90.15**	0.15
US	**1·55**	**1·27**	**1·90**	**0·00**	**1·79**	**1·30**	**2·48**	**0·00**	**1.42**	**1.34**	**1.51**	**16.97**	0.10
Family history	1·31	0·84	2·08	7·71	1·31	0·70	2·44	23·85	1.48	0.85	2.53	0.00	0.37
BMI	1·01	1·00	1·02	15·14	1·01	0·99	1·03	0·00	**1.03**	**1.02**	**1.04**	**77.20**	0.14
Tardive dyskinesia	**2·39**	**1·05**	**5·42**	**0·00**	**5·16**	**1·55**	**17·12**	**0·00**	**Inf**	**Inf**	**Inf**	**100**	0.08
Akathisia	1·73	0·95	3·16	15·93	**2·89**	**1·15**	**7·24**	**0·00**	**Inf**	**Inf**	**Inf**	**100**	0.12
Parkinsonism	1·25	0·94	1·67	0·00	1·34	0·76	2·36	0·00	Inf	0.00	Inf	100	0.16
Nicotine smoking	**1·20**	**1·02**	**1·40**	**0·00**	1·22	0·93	1·62	0·00	Inf	0.00	Inf	100	0.22
Substance use disorder	**1·55**	**1·15**	**2·10**	**0·00**	**2·36**	**1·39**	**4·01**	**0·00**	**1.36**	**1.34**	**1.39**	**0.00**	**<0.01**
Age at diagnosis	**0·97**	**0·96**	**0·99**	**43·61**	**0·97**	**0·96**	**0·99**	**0·00**	**1.02**	**1.01**	**1.02**	**0.00**	0.14
Duration of illness	1·00	1·00	1·01	0·00	1·01	1·00	1·02	0·00	**1.02**	**1.01**	**1.02**	**0.00**	0.32
CGI	**1·28**	**1·12**	**1·48**	**57·28**	1·11	0·92	1·34	35·36	**1.21**	**1.06**	**1.38**	**0.00**	0.14
Personal and social performance scale	**1·01**	**1·01**	**1·02**	**6·52**	**0·98**	**0·97**	**0·99**	**0·00**	1.02	1.00	1.04	67.99	0.32
Total psychopathology	1·01	1·00	1·01	36·00	1·00	0·99	1·01	13·77	1.01	1.00	1.02	0.00	0.14
General psychopathology	1·01	0·99	1·02	40·36	1·00	0·98	1·02	32·97	1.01	1.00	1.02	29.36	0.14
Positive psychopathology	**1·04**	**1·02**	**1·06**	**44·59**	1·04	0·99	1·08	44·81	**1.02**	**1.01**	**1.04**	**32.42**	0.14
Negative psychopathology	0·99	0·98	1·01	0·01	0·99	0·96	1·01	0·00	**1.02**	**1.01**	**1.04**	**7.36**	0.15

Legend: CI=Confidence Interval; US=United States; TD=Tardive dyskinesia; EPS=Extrapyramidal symptoms; BMI=Body Mass Index; CGI=Clinical Global Impressions Severity score; PANSS=Positive And Negative Syndrome Scale

Figure 1. Pooled incidence rates of relapse during continuous antipsychotic treatment

Fig 1a

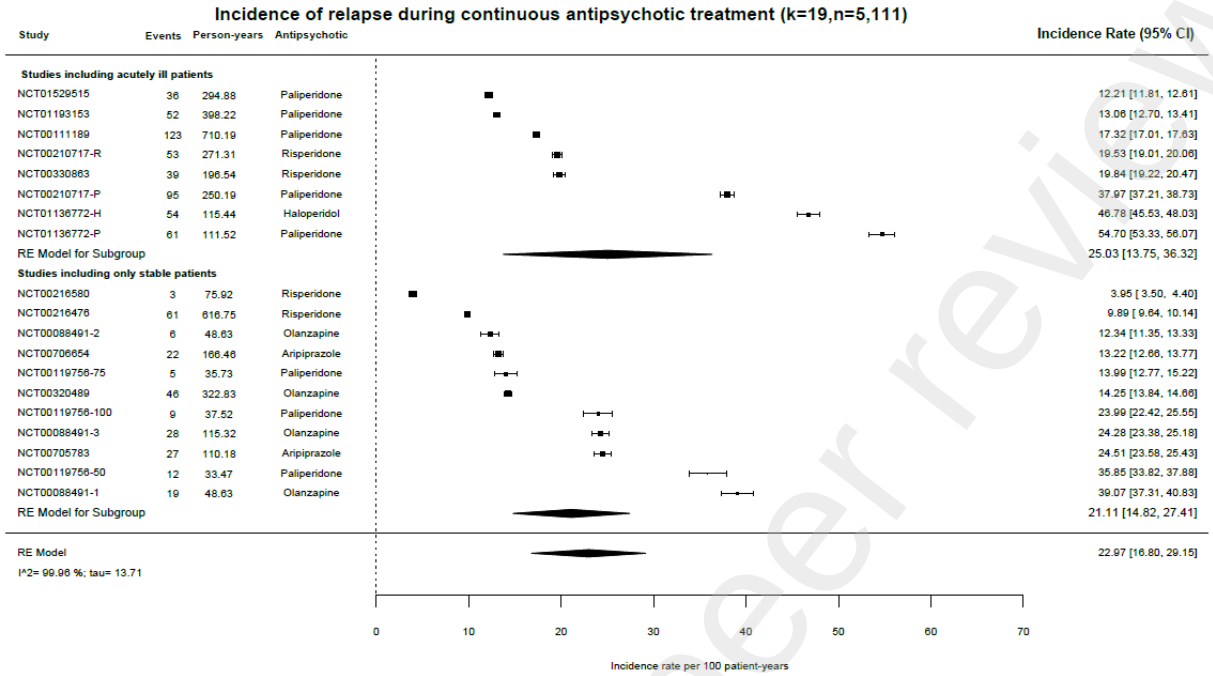


Fig 1b

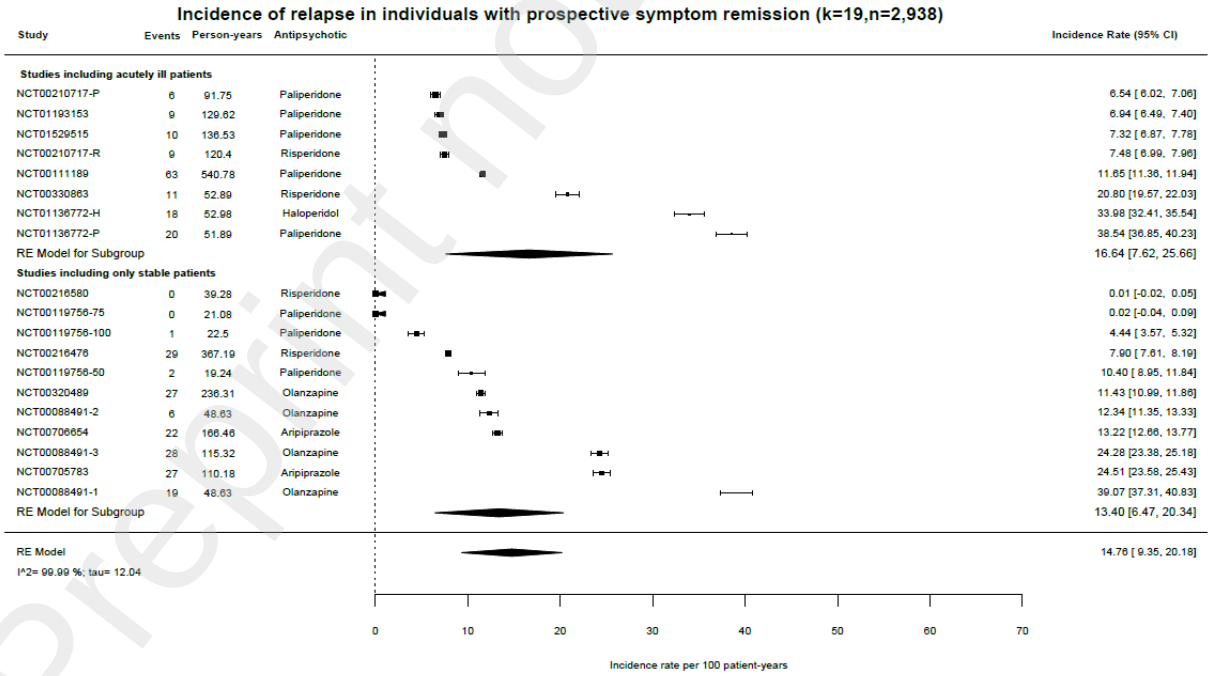
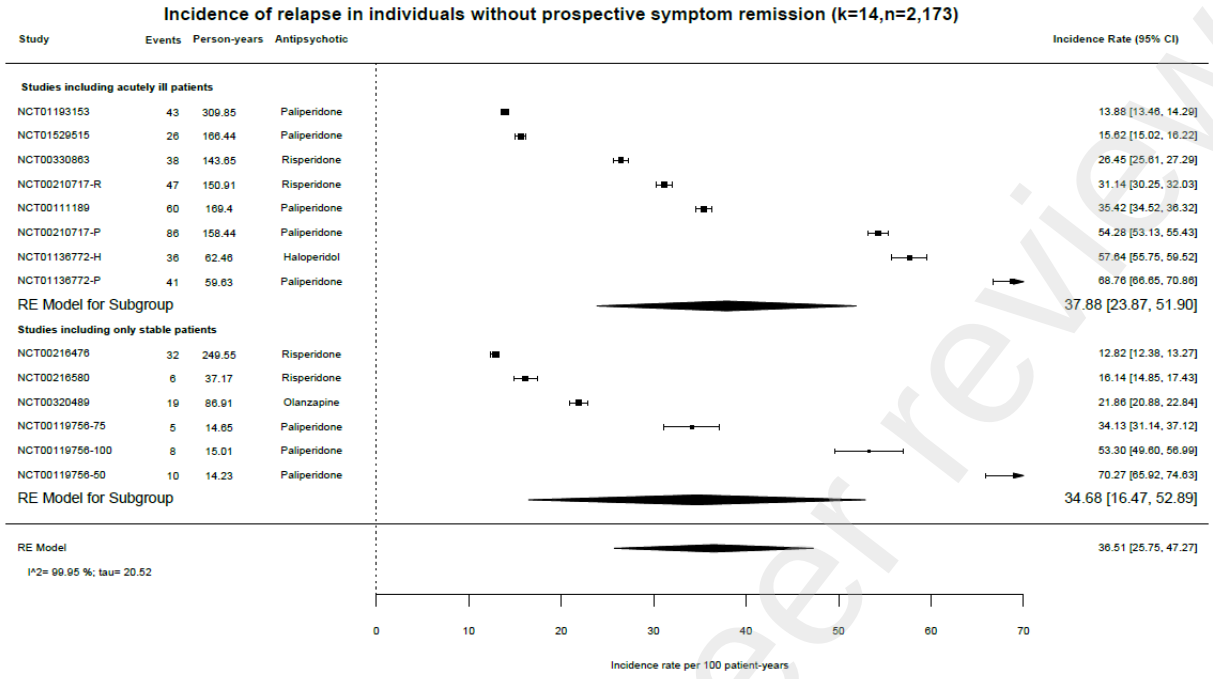


Fig 1c



Legend: Pooled incidence rate of relapse among individuals with schizophrenia-spectrum disorders during antipsychotic treatment confirmed by long acting injectable formulations in 1a) total cohort of 5,111 individuals treated for sufficient time to achieve therapeutic plasma level, 1b) Sub-cohort of individuals who demonstrated prospectively symptom remission, 1c) Sub-cohort of individuals who did not demonstrate prospectively symptom remission.

Figure 2. Psychosis relapse over time during continuous antipsychotic treatment

Fig 2a

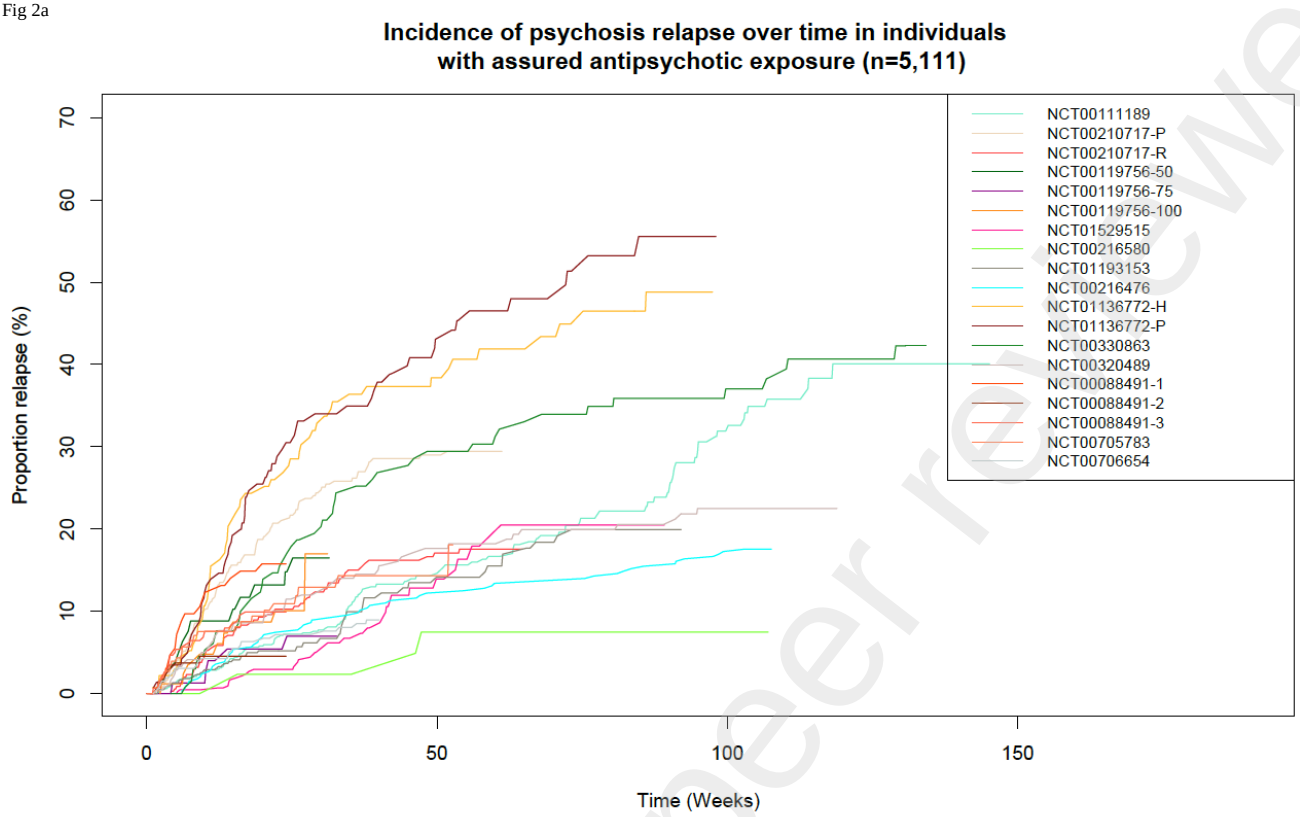


Fig 2b

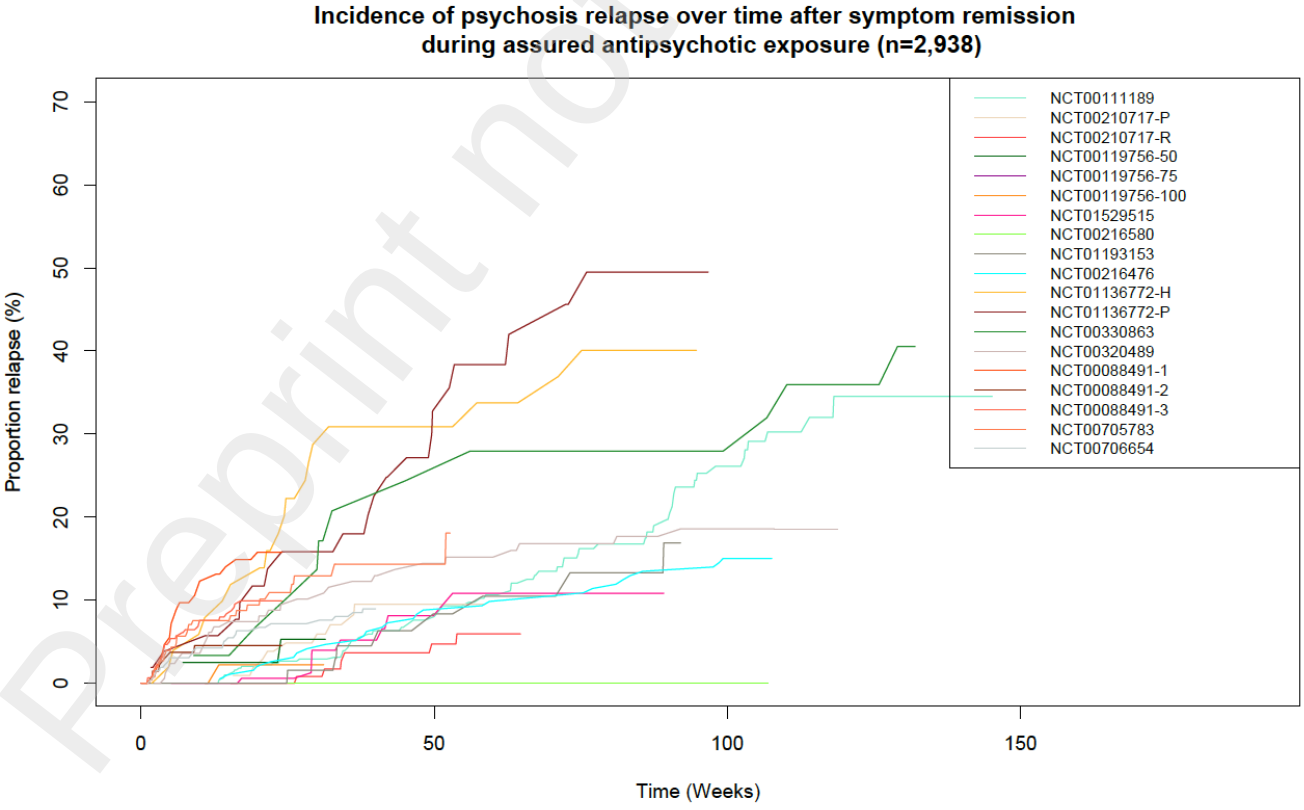
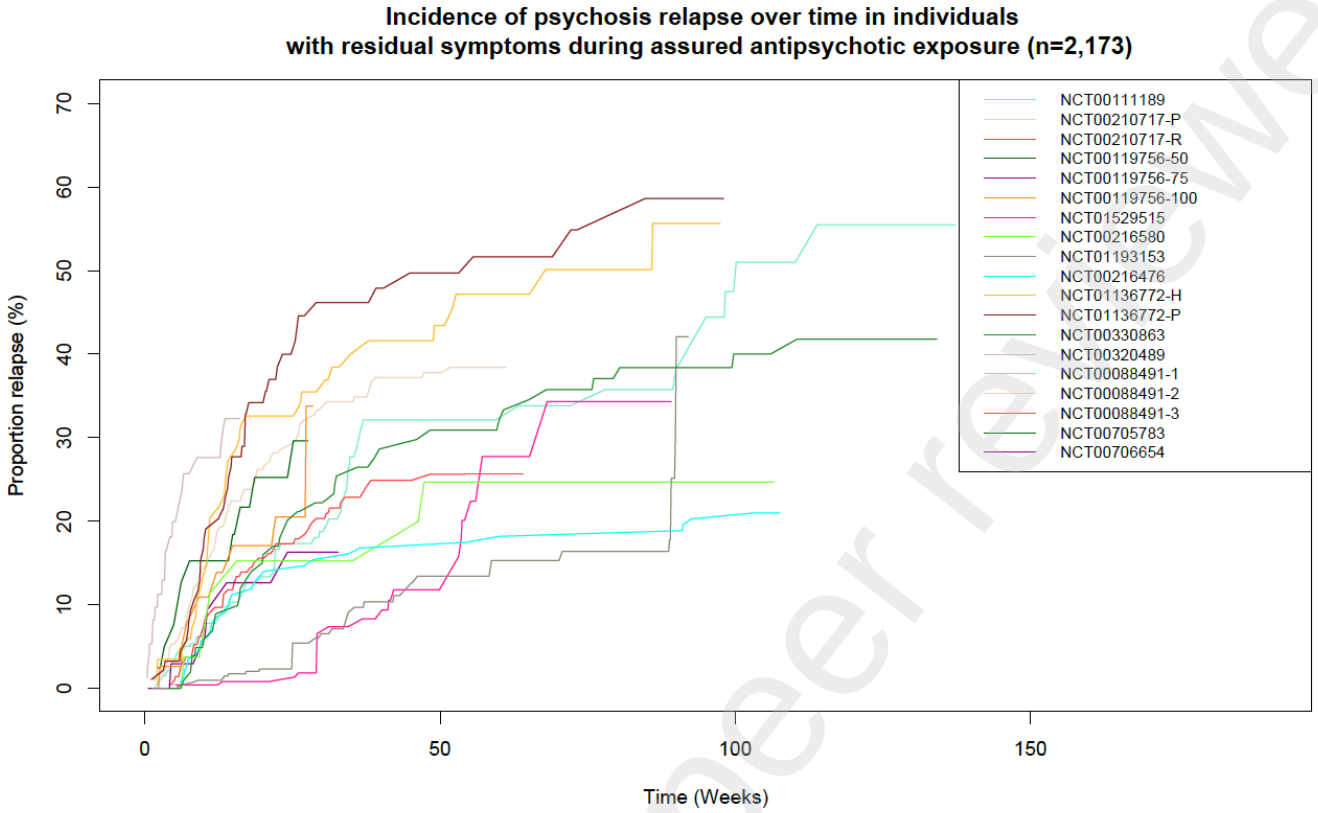


Fig 2c



Legend: Curves of incidence of relapse over time among individuals with schizophrenia-spectrum disorders during antipsychotic treatment confirmed by long acting injectable formulations in 2a) total cohort of 5,111 individuals treated for sufficient time to achieve therapeutic plasma level, 2b) Sub-cohort of individuals who demonstrated prospectively symptom remission, 2c) Sub-cohort of individuals who did not demonstrate prospectively symptom remission.