Recommendations for defining treatment outcomes in major psychiatric disorders leveraging real-world data

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Abstract

While information from real-world data (RWD) can be utilized to identify factors able to aid treatment choice, guidelines for the use of RWD are lacking. The aim of this narrative review and expert opinion is to summarize and evaluate definitions of treatment outcomes to antidepressants, antipsychotics, and mood stabilizers using RWD, and to suggest standards for the field. Given that no standards for the use of RWD in estimating treatment outcomes exist, there is a high variability in treatment outcome definitions. We make recommendations for different scenarios of available data and highlight the importance of using other sources of information to validate proxy phenotypes such as continued treatment, switching between medications or polypharmacy of psychotropic medications. Well-defined and validated treatment outcome measures leveraging RWD hold the potential to facilitate the development of precision psychiatry approaches and support regulatory decision-making in psychopharmacological agents.

Research in context

Evidence before this study
There are massive amounts of real-world healthcare data with treatment outcomes that can be applied in data-driven research to identify factors related to outcome, with the ultimate goal of improving pharmacotherapy in psychiatry. Moreover, real-world data can be implemented for pharmacovigilance and drug repurposing to support regulatory decision-making. To review the literature on pharmacological treatment outcome definitions from real-world data that have been used for schizophrenia, bipolar disorder, and major depression, PubMed was used to identify articles (up to August 1, 2024) on "real-world data AND [antidepressants OR antipsychotics OR mood stabilizers]," "real-world data AND precision psychiatry," "electronic health records AND [precision psychiatry OR antidepressants OR antipsychotics OR mood stabilizers]," and "treatment stratification AND psychiatry AND [real-world data OR electronic health records]". The literature review showed that there is a high variability in treatment outcome definitions, and research findings are difficult to compare. Further, guidelines for estimating treatment outcomes from health registries, hospital records, and self-reports are lacking. Given that no standards for using real-world data exist, there is high variability in treatment outcome definitions, and findings are difficult to compare or meta-analyze.

Added value of this study
We have reviewed the current literature and presented the different outcome measures applied in previous studies. Building on these findings, we have made recommendations for different real-world scenarios and available data. This is the first attempt to define outcome measures using real-world data, which will form the starting point of a series of studies that can form the basis of an iterative process improving the definitions. We highlight the importance of validating proxy phenotypes using other sources of information. We conclude that well-defined and validated treatment outcome measures leveraging real-world data have the potential to form the basis for developing precision psychiatry approaches and support regulatory decision-making on psychopharmacological treatment.

Implications of all the available evidence

With the growing interest in AI-tools, there is a need for large training and test data from health care with better quality. Standardization of treatment outcome definitions is important for leverage current research aiming to develop prediction and stratification tools for future precision psychiatry.

Introduction

The treatment of psychotic and affective symptoms, which are core characteristics of the severe mental disorders schizophrenia (SCZ)[1], bipolar disorder (BIP)[2] and major depressive disorder (MDD)[3], remains a significant challenge in psychiatry. Current medications for SCZ mainly include antipsychotics[1], and antidepressants are the main medications used to treat MDD[3]. While BIP is primarily treated with lithium and other mood stabilizers[2], the treatment of BIP is particularly challenging as the different phases of the disorder need different treatment approaches[4]. Although psychotropic medications are effective for the majority of patients with psychiatric disorders[5], there is a large variation in their efficacy and adverse effects[6]. Individuals whose symptoms do not meaningfully improve after ≥2 psychotropic drug trials of adequate dose and duration are commonly defined as having treatment-resistant or difficult-to-treat conditions[6]. Non-response to psychotropic medication is a significant clinical problem, with failure rates of around 30% in SCZ[7, 8], BIP[9], and MDD[3, 10]. However, the rates of treatment resistance are difficult to determine in BIP, as they differ in maintenance and acute manic, depressed, or mixed states[4, 11], with depression being associated with greater risk of relapse than mania[4, 12]. For MDD, the estimated rate of treatment resistance increases to about 55% when emphasizing symptomatic remission in the definition of antidepressant treatment resistance[10].

Adverse effects to psychotropic medication are common and often cause non-adherence or discontinuation leading to relapse and increased risk for suicide[13-15]. For antipsychotics, major adverse effects include sedation, weight gain, and motor side effects[1, 13, 14]. Common adverse effects of antidepressants include headache, anxiety, agitation, gastrointestinal symptoms, and loss of libido[16]. For mood stabilizing treatment, tremor, cognitive impairment, and weight gain are common adverse effects[2]. Additional complexity arises from the common use of polypharmacy in psychiatry, increasing the risk for adverse effects and drug-drug interactions[17, 18]. Guidelines offer limited support for medication choice, given the lack of specific treatment indications and under-exploitation of real-world data (RWD) for treatment outcomes[19]. Therefore, psychopharmacological treatments often follow a trial-and-error principle, attempting to balance between therapeutic and adverse effects[20]. Existing information from RWD can be leveraged to identify factors able to aid treatment choice, to improve treatment response and reduce adverse effects.

RWD is defined by the US Food and Drug Administration (FDA) as “the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources”[21]. The European Medicines Agency (EMA) defines RWD as “routinely collected data relating to a patient’s health status or the delivery of health care from a variety of sources other than traditional clinical trials”[22]. According to the European Medicines Regulatory

Network (EMRN) strategy, by 2025, the use of RWD will have been enabled and the value of RWD will have been established across regulatory use cases, to support the development and use of better medicines for patients[23, 24]. RWD from health registries and hospital records/electronic health records (eHRs), laboratory databases, as well as self-reported drug use and related treatment response can provide large-scale data to study treatment outcomes in psychiatric disorders. From nationwide prescription records, treatment response can be estimated from proxy phenotypes, for example based on the duration and changes in type and dosage of medication[25]. These data sources are essential for the advancement of precision medicine treatment in psychiatry, as they provide the large-scale data needed to develop and validate clinical prediction models of treatment outcomes[26].

As illustrated in **Supplementary Figure 1** (Appendix), RWD have the potential to both facilitate precision psychiatry and to support regulatory decision-making on psychopharmacological treatment. However, no standards exist for use of RWD to analyze treatment response, and there is high variability in treatment outcome definitions using RWD. In randomized controlled trials (RCTs) or other clinical studies, treatment response is standardly assessed using disease specific rating scales and treatment adherence is closely monitored. In contrast, RWD are subject to high variability and confounders, especially when proxy phenotypes are used to estimate treatment outcomes. Improvement of using proxies in large datasets and standardization of treatment outcome measures using RWD is therefore needed. The aim of this narrative review and expert opinion is to summarize and evaluate definitions of treatment outcomes to antidepressants, antipsychotics, and mood stabilizers using RWD, and to propose standards for the field.

Methods

To review the literature on pharmacological treatment outcome definitions from RWD that have been used for SCZ, BIP, and MDD, PubMed was used to identify articles (up to August 1, 2024) on "real-world data AND [antidepressants OR antipsychotics OR mood stabilizers]," "real-world data AND precision psychiatry," "electronic health records AND [precision psychiatry OR antidepressants OR antipsychotics OR mood stabilizers]," and "treatment stratification AND psychiatry AND [real-world data OR electronic health records]". We searched the literature to qualitatively evaluate relevance to the current objective and selected papers based on their relevance for treatment outcome measures to be included in a non-systematic narrative review. We brought together a group of international experts (including psychiatrists, pharmacologists, employees of pharmaceutical companies, and researchers with extensive experience in working with RWD). Coordinated by the lead author, we had monthly online meetings from November 2023 to September 2024 to discuss evidence, select articles to be included in the narrative review, and to make recommendations for treatment outcome definitions. We finalized our recommendations at an in-person meeting in October 2024. Using expert opinion, we evaluated treatment outcome measures using RWD, suggested validation for proxy phenotypes and proposed plans for better use of currently available data.

Definitions of treatment outcomes from real-world data: Challenges and opportunities

Guidelines to define pharmacological treatment outcomes in psychiatry are mostly based on clinical measures such as symptom rating scales, which are widely applied in clinical studies[6]. While guidelines for the use of RWD are lacking, proxy measures such as continued treatment, switching between psychotropic medications or polypharmacy have been applied to assess treatment outcomes. Definitions used for these proxy measures of pharmacological treatment outcomes using RWD in MDD, SCZ, and BIP are summarized in **Supplementary Table 1** (Appendix).

Antidepressants

To define treatment outcomes in MDD, switching between antidepressant drugs has been widely applied as a proxy for non-response in RWD research[27-35], although switching can result from both lack of treatment effect and adverse effects. Treatment-resistant depression (TRD) is widely used as an outcome variable, broadly defined as ≥2 switches between antidepressant drugs prescribed for an adequate duration in individuals diagnosed with a depressive disorder[10, 27, 28, 30-36]. In some studies, both duration and dose have been considered[28, 32, 33]. However, the criteria for defining adequate dose and duration vary between studies. In other studies, TRD has been defined based on use of electroconvulsive therapy (ECT) derived from register data or medical records[37-39]. Using RWD, treatment stability has been defined as continued prescription of an antidepressant, for example for ≥90 days, as a proxy for treatment effectiveness[40]. In contrast, the time needed to assess treatment response in clinical trials is 4-12 weeks[15]. Antidepressant duration as a continuous measure, in terms of number of prescriptions or weeks of prescription, was used as a proxy for antidepressant response based on UK Biobank data, in addition to various measures of antidepressant switching and discontinuation[41]. Treatment response has also been defined by using eHRs from a clinical register that gathers clinical information across hospitals, where clinical notes were used to identify evidence of improvement applying a deep learning-based text classification model[42]. Using a similar approach, TRD has been defined as ≥2 depression-related visits within a 12-month period following an initial antidepressant prescription and ≥2 antidepressants during this period, using eHRs[43]. In a genome-wide association study (GWAS), both antidepressant switching and questionnaire data have been used to define TRD, and questionnaire data was used to define antidepressant response[44]. In that study[44], TRD was defined as non-response to ≥2 antidepressants taken for at least 5–6 weeks, and non-TRD was defined as response to either the first or second medication taken for at least 3–4 weeks[45]. In most other studies on TRD, the non-TRD group includes all individuals not meeting the criteria for the TRD group. In a recent GWAS on antidepressant non-response, data from rating scales for depressive symptoms, questionnaires of treatment effect, and data from eHRs have been combined to increase sample size[46]. However, switching antidepressants may be independent from response, for example at least in some cases it may be due to side effects or lack of compliance. It should also be noted that antidepressant continuation is not always a reliable indicator of response but could reflect inertia or lack of clinical follow-up despite poor response[33, 47]. Moreover, different antidepressant classes are often grouped into one analysis category, but, even within the same class, antidepressants may differ considerably in their mechanism of action[3]. Furthermore, antidepressants are frequently prescribed for conditions other than depression, highlighting the importance of supplementing with diagnostic information, which is not always considered in RWD-based studies. In addition, co-morbidities may be underlying the development of TRD. It has been shown that individuals with comorbid posttraumatic stress disorder (PTSD) were less likely to achieve remission from MDD after antidepressant treatment[48]. Other factors that could increase the risk of developing non-remission after antidepressant treatment include hospitalization for suicide crisis, attempts or other episodes of self-harm[49, 50].

Antipsychotics

Previous studies investigating treatment outcomes in SCZ have mainly focused on treatment-resistance. Clozapine is the only evidence-based medication for treatment-resistant SCZ, which is characterized by a failure of response to at least two antipsychotic trials of adequate dose and duration[8, 51]. As it is primarily used for treatment-resistant SCZ, clozapine has been widely used in research as a proxy measure for non-response/treatment resistance both using clinical data and RWD[6, 8]. In a study using eHRs, treatment-resistant SCZ was defined as either use of clozapine or prescription of a third new antipsychotic after two different antipsychotic prescriptions for ≥6 weeks[52]. Use of clozapine or antipsychotic polypharmacy defined as ≥2 antipsychotics for ≥90 days has been used as a proxy for treatment-resistant SCZ in a Swedish register study[53]. However, prescribing guidelines stating that polypharmacy should only be considered after first trying clozapine are not consistently applied in clinical practice[54]. Therefore, inclusion of polypharmacy as a criterion for treatment-resistant SCZ may increase the number of false positives. Another issue is potential pseudo-resistance, where lack of response can result from sub-therapeutic medication levels due to poor adherence or metabolic status[55, 56], supporting the utility of therapeutic drug monitoring (TDM). In Danish population registry data, treatment-resistant SCZ was defined as clozapine initiation or hospitalization due to SCZ during antipsychotic treatment within 18 months after ≥2 periods of different antipsychotic monotherapies, each lasting ≥6 weeks[57, 58]. Both cases receiving clozapine and those who were not treated with this drug but still showed evidence of poor response to multiple antipsychotics are captured in these phenotypes of resistance. In a study using the UK mandatory monitoring system for clozapine users, treatment-resistant SCZ was defined as a clinician reported diagnosis of treatment-resistant SCZ[59]. There are several considerations when using clozapine as a proxy phenotype for non-response or treatment resistance. The control group (individuals with SCZ who never used clozapine) could still include individuals with poor treatment response or resistance, as clozapine is prescribed only to a fraction of patients with non-response to ≥2 antipsychotics[60]. Moreover, clozapine prescription rates differ by country[61], sex[62] and ethnicity[63]. Finally, a minority of patients eligible for clozapine starts this treatment, mostly for issues linked to side effects and the need for regular blood monitoring[64]. Using data from eHRs, ultra-treatment-resistant SCZ (i.e. non-response to clozapine) has been defined as readmission following an inpatient episode where the patient was discharged on clozapine[65]. Moreover, hospitalization or an emergency department attendance has been widely used as a proxy for relapse when using eHRs[66-68]. One of these studies attempted to remove nonadherent patients, by excluding those who had fewer than 90 days of stable prescription of antipsychotic monotherapy before the study start date[68]. However, these studies may include hospitalization or emergency department attendance for other reasons such as drug-induced psychosis or suicide attempts.

Lithium and other mood stabilizers

BIP is characterized by episodes of distinct groups of symptoms[2], and its treatment is more multimodal compared to MDD and SCZ[2, 4], making treatment outcomes more difficult to define. Previous studies investigating treatment outcomes in BIP mainly include studies of lithium response assessed by the Alda scale ("Retrospective Criteria of Long-Term Treatment

Response in Research Subjects with Bipolar Disorder")[69], and consensus definitions of treatment outcomes in BIP are based on the use of clinical assessments[4, 11, 70]. In cohorts where clinical information such as symptom rating scales is not available, registry data has been used to define lithium non-response, to find alternative definitions to those based on clinical evaluation. In a nationwide register-based study from Denmark[71], lithium non-response was defined as hospitalization at a psychiatric ward or prescription of a second psychotropic drug within six months after starting lithium treatment, whereas lithium monotherapy for more than six months without hospitalization was considered as indicative of response. Questionnaire data have also been used to define lithium response[72]. However, data on subjective treatment outcomes may be biased by factors such as comorbid disorders and treatment non-adherence, which should be considered when defining treatment outcomes[4]. This has been demonstrated in a study assessing factors associated with self-perceived treatment-resistance in BIP, showing that a large proportion of patients had symptoms of comorbid mental disorders that were regarded as treatment-resistant bipolar symptoms while other patients did not receive adequate treatment or did not adhere to the treatment[73]. Recent results from the SUPER-Finland psychosis study have shown that a group of severely affected individuals with BIP later received the diagnosis of SCZ[74], suggesting that initial misdiagnosis can confound the interpretation of failed treatment response in RWD. Moreover, experts have proposed that lithium response should be defined in the context of level of lithium exposure, e.g., dose, treatment duration, adherence, plasma levels, and adjunctive treatments[75]. Using eHR data, treatment failure of mood stabilizers has been defined as time to discontinuation of the medication or add-on of another mood stabilizer, antipsychotic, antidepressant or benzodiazepine[76]. However, bipolar depressive episodes are often treated with off-label medications, and it has been argued that definitions similar to those used for unipolar depression should be avoided, because the pathogenesis of bipolar depression are different from unipolar depression[77]. Other outcome measures such as occupational dysfunction and hospital admissions may be a preferable proxy phenotype for non-response to maintenance treatment in BIP, because these are indicative of relapse[78].

Definitions of treatment outcomes from real-world data: Expert opinion and recommendations

RWD from health registries and hospital records/eHRs as well as self-reports can provide large-scale data needed for prediction and stratification of treatment outcomes in psychiatry research[26]. However, RWD are subject to variability and confounders, requiring careful curation and validation to increase the specificity of treatment outcome measures. RCTs are considered the gold standard for assessing treatment effects, as patients are randomly assigned to receive an intervention[79] and provide longitudinal symptom measures to examine change across time with a particular treatment. However, RCTs may not be representative of the whole clinical population[80], a known fact leading to the over-estimation of the effects of many drug treatments in comparison to real-world scenarios[81]. Patients in RCTs are generally healthier than in the real world, in part because of the need for informed consent, which can be difficult to obtain during the acute phase of the illness. Individuals with psychiatric and somatic co-morbidities who are treated with several drugs (polypharmacy) are usually excluded from RCTs, because they are at greater risk of developing drug-drug interactions and adverse effects. Similarly, suicidal ideation, substance use, and advanced age are commonly considered exclusion criteria. In addition, treatment adherence is better in RCTs than in the real world[82]. Thus, RWD provide a unique opportunity to validate findings from RCTs (short term, monotherapy) in real-world settings (long term, co-morbidities, polypharmacy)[83], e.g., to study the long-term effects of ketamine/esketamine in TRD that are still not fully known[84, 85]. Moreover, RWD can be complementary to RCT to evaluate treatment effectiveness, because RWD reflect the reality of health care, providing insights into trajectories of pharmacotherapy and both psychiatric and somatic co-morbidities[26].

However, the complex and heterogeneous nature of RWD makes it challenging to define treatment outcomes. Heterogeneity in RWD may arise from a variety of differences between countries, health care systems, practitioners, and type of data source (primary care, specialist care, hospitals). In addition, RWD from any single source, e.g., from prescription registries, may be incomplete and unstructured. Linkage to other registries can help refine treatment outcome definitions based on prescription registry data by incorporating additional information such as hospitalization during pharmacological treatment. In the Nordic countries, including Denmark, Finland, Iceland, Estonia, Norway, and Sweden, prescription databases can be linked to other health registries[86]. Studies based on the Nordic prescription databases have yielded new knowledge on the beneficial and adverse effects of drug use in real-world settings[25]. Routinely collected information in eHRs and population-wide health registries can provide information about diagnosis and co-morbidities, but also sociodemographic information and functional outcomes such as cause of death, sick leave and employment status, hospitalizations, as well as anthropometric and blood measures such as lipid levels. Linking these data to prescribed drugs for longitudinal observations, can provide proxies for treatment outcomes such as wellbeing and functioning as well as adverse effects from specific drugs, e.g., weight gain[87], hypertension or hyperlipidemia.

For the definition of proxy phenotypes of treatment response using prescription registries, it is important to consider diagnostic information, dose, duration of treatment, and information about the indication for drug prescription. Whereas diagnostic information can be retrieved from other health registries, and dose and duration can be derived from the prescription registry, information about indication is often missing on prescriptions. However, diagnostic information can serve as a proxy of the indication of psychotropic medications. While diagnostic information in registries from the International Classification of Diseases (ICD) may be subject to variability, clinical validation of registered diagnoses has demonstrated high consistency with diagnoses based on structured interviews, indicating that registry data can provide reliable diagnostic information[88, 89]. Moreover, the indication of psychotropic medications can often be estimated from the dosage of the drug, e.g., it is common to use low-dose of some antidepressants for sleep[90] or low-dose of antipsychotics to treat behavioral and psychological symptoms in dementia[91], so these prescriptions should not be considered as treatment of MDD, BIP, or SCZ. Natural language processing (NLP)[92] can be applied to free text in prescriptions and can also be used to retrieve information on the indication of the prescribed drug. NLP, through the development of artificial intelligence algorithms known as language models, is also well-suited for extracting information from general text records[92], and can thus be used for extraction of free text from unstructured routine health data to capture symptom improvement or other more complex treatment-related phenotypes. When using prescription registries where dose information is missing, the daily dose can be calculated from the amount of the purchased drug and time between purchases. It has been shown that information from these dose calculations can be used to address clinically useful research questions on antipsychotic treatment outcomes[93]. It has also been shown that proxies of poor compliance to antidepressant treatment can be calculated by the proportion of adequate prescription intervals, defined by 14 weeks or less between subsequent antidepressant prescriptions[27].

It should be noted that treatment outcome measures derived from RWD such as prescription registries are still proxy phenotypes, even though various RWD sources are combined to refine these proxy measures. Moreover, there are potential limitations that are difficult to address, e.g., the use of diagnostic information as a proxy of the indication of psychotropic medications may be biased by co-morbidities such as PTSD or borderline personality disorder. However, it is an advantage that these individuals are not excluded when defining treatment outcome measures as they relect real-world settings. Another confounder in defining treatment outcome measures from RWD that remains difficult to address is immortal time bias, referring to a period of follow-up during which death or the study outcome cannot occur[94]. Therefore, it is important to consider treatment duration in both the group defined as non-responders or treatment resistant and the group defined as responders or non-treatment-resistant, to minimize errors in estimating the association between treatment and outcome[95]. Our recommendations for defining treatment outcomes in major psychiatric disorders leveraging population-wide health registries and routinely collected questionnaires/self-reports are summarized in **Tables 1-3** and **Boxes 1-3**. Recommendations for measuring psychopharmacological treatment outcomes using free text from electronic health records are summarized in **Supplementary Table 2** (Appendix). These recommendations are suggestions for better use of proxy measures. When applying switching between psychotropic medications as a proxy measure of treatment resistance, the medication class has not been considered in our recommendations. While other authors have suggested the use of a definition based on different classes of antipsychotics or antidepressants, there is no convincing evidence supporting a definition involving different classes[6]. The definition of TRD involving different antidepressant classes is not supported by many consensus guidelines, including EMA[10, 96, 97]. We make recommendations for different RWD sources to achieve improved outcome measures. For example, when using treatment duration of ≥6 weeks as a criterion to define antidepressant switching as a proxy for non-response, switches due to side effects will be reduced while some side-effects-related switches may also occur after 6 weeks. Likewise, stable treatment with the same drug does not always reflect treatment response. Therefore, validation of proxy measures becomes important to evaluate the potential of RWD for clinical application. Whereas definitions of TRD from RWD have been compared with definitions from clinical data[98, 99], findings from studies using RWD to define and predict treatment outcomes should be replicated and validated using other sources of information such as questionnaires. In the Estonian Biobank[100, 101], data from prescription and other registries as well as questionnaire data on treatment response is available, thus definitions of treatment response using prescription registry data can be validated using the questionnaire data. In Finland, the Social Insurance Institution of Finland's national medical drug purchase registry can be used to define treatment outcomes, which can be validated in the recently recruited SUPER-Finland psychosis study[102]. Convincing results from the SUPER-Finland study have shown that longitudinally tracking psychiatric hospital burden is a feasible method to assess longitudinal disease trajectories. Psychiatric hospital burden was strongly associated with RWD measures such as clozapine use, global function at discharge, and cognitive performance[74]. These results suggest that response to drug treatment could be adequately assessed using linked registry data. In a recent study, Patient Health Questionnaire scores have been used for validation of proxy phenotypes of antidepressant treatment outcomes, showing that antidepressant switching and treatment with add-on medications were strongly associated with higher depression severity scores[103]. Other samples that can be used for validating treatment outcome definitions from RWD include quality registries such as the Swedish National Quality Register for bipolar disorder[81] that contain data on patient problems, medical interventions, and outcomes after treatment, the UK Biobank[104] that includes mental health and treatment response questionnaires, and the All of US Research program[105] including multitudinous data from eHRs and questionnaires. Moreover, it should be investigated how the definitions differ among countries, e.g., the proportion of individuals that fall under a specific definition, to determine if proxy measures of treatment outcomes from RWD are comparable across countries. Taken together, RWD from registries and health care systems with potential for record-linkage combined with questionnaire data and self-reports on medication response and adverse effects could provide clinically useful treatment outcome measures in major psychiatric disorders.

It is widely accepted that RWD are more generalizable than evidence from standardized clinical trial data, because RWD more likely reflect real treatment effects[106]. Regulatory agencies such as EMA have increasingly considered the use of RWD to support regulatory decision-making complementary to evidence from RCTs[107, 108]. To date, RWD has been used primarily in post-approval settings to monitor drug safety and detect adverse events as well as to support dose modifications, and it has been stated that RWD are useful in assessing the feasibility of new indications[107-109]. RWD can be leveraged to capture long-term treatment outcomes to complement RCTs to evaluate safety and effectiveness, especially when the treatment outcomes and related safety require longer follow-up durations, e.g., functional outcomes, hospitalization, and suicide. In a Swedish registry study[110], it has been demonstrated that patients with attention deficit–hyperactivity disorder (ADHD) had reduced rates of criminality when receiving ADHD medications[110]. Another Swedish registry study showed that patients with BIP receiving antidepressant monotherapy had an increased risk of mania compared to patients receiving an antidepressant in combination with a mood stabilizer[111]. Moreover, RWD could provide additional evidence to support regulatory decision-making for new indications of existing drugs, known as repurposing. Computational drug repurposing for psychiatric disorders has gained increasing interest in research[112-116]. However, it has been difficult to validate the effectiveness of the suggested repurposing candidates in psychiatric disorders. RWD such as lifetime health registries could be used to screen for associations between use of repurposing candidates and reduced risk of psychiatric disorders[117] as well as for characterization of treatment outcomes including long-term outcomes such as hospitalization and suicide as well as health-economic aspects such as sick leave. Before implementing RWD for pharmacovigilance and drug repurposing, the outcome measures must be well-defined and validated in research. For research using RWD, privacy protection for individuals contributing to RWD must be addressed by data protection legislation[118]. Secure data systems for Trusted Research Environments (TRE) must be implemented to ensure that the RWD are impossible to identify and the data are securely handled, e.g., in the UK, OpenSAFELY (https://opensafely.org/) is a TRE where approved researchers never have direct access to real data. In Europe, secure data handling environments must align with requirements from the GDPR and upcoming European Health Data Space (EHDS), particularly when databases are cross-linked.

Conclusion

RWD from different sources has the potential to both solve the need for large-scale data and provide treatment outcome measures that can be applied in research aiming to improve pharmacotherapy in mental disorders. The definition of proxies for treatment outcomes can be improved by integrating RWD from various registries and health care systems that can be linked to questionnaire data and self-reports on medication response and adverse effects. We make recommendations for different scenarios and available data and highlight the importance of validating proxy phenotypes using other sources of information such as questionnaires. Well-defined and validated treatment outcome measures leveraging RWD have the potential to facilitate precision psychiatry and support regulatory decision-making on pharmacological treatment in psychiatry.

Contributors

OAA conceived the study. EK drafted the initial manuscript. All authors contributed to the interpretation and editing of the manuscript.

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Declaration of interests

Dr. Andreassen has received speaker fees from Lundbeck, Janssen, Otsuka, and Sunovion and is a consultant to Cortechs.ai. and Precision Health. Dr. Lewis sits on the Scientific Advisory Board for Myriad Neuroscience. Dr. Serretti has served as a consultant or speaker for Abbott, Abbvie, Angelini, AstraZeneca, Clinical Data, Boehringer, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Innovapharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi, and Servier and Taliaz. Dr. Molden has received speaker's honoraria from Lundbeck and Otsuka. Dr. Dawson is the owner of P1vital LTD. Dr. Einarsson, Dr. K. Stefánsson, and Dr. H. Stefánsson are employed at deCODE genetics, subsidiary of Amgen.

Table 1: Recommendations for measuring treatment outcomes in major depression using real-world data

RWD sources	Phenotype	Criteria
Population-wide health registries	Diagnosis	Diagnosis of MDD is required and should be obtained from specialist (alternatively primary) health care (ICD10).
	Antidepressant treatment	Medication use from prescription registry: ATC codes N06A, as well as ketamine (N01AX03) and esketamine (N01AX14).
	Indication	Indication can be extracted from free text of prescriptions. Other indications than depression (e.g., pain or sleeping problems) should not be considered as antidepressant treatment.
	Antidepressant switching	Medication use from prescription registry (ATC codes N06A): To define TRD, it should be ≥2 antidepressant switches, and each switch should between 6 weeks (for adequate treatment duration) and 14 weeks (to exclude treatment interruption) of the previous antidepressant prescription.
	Augmentation/ combination therapy	Augmentation of or combination with another antidepressant or antipsychotic or lithium.
	Stable treatment	Treatment for ≥6 months.
	Adequate treatment duration	Obtained from prescription registry: Should be ≥6 weeks to reduce the risk of switches due to side effects.
	Adequate dose	Daily dose from prescription registry: Should have minimal dose recommended for major depression.
	Hospitalization	Hospitalization due to a depressive episode; should be during or shortly after antidepressant treatment.
	Comorbidity	Other psychiatric diagnoses should be excluded if these are the main diagnosis or exclude the diagnosis of MDD (e.g., BIP).
	Neurostimulation (ECT or TMS)	Neurostimulation should be during or shortly after antidepressant treatment.
	(Es)ketamine treatment	Treatment with ketamine/esketamine should be during or shortly after antidepressant treatment.
	Adherence	Ratio between prescribed and dispensed medication can be calculated to estimate adherence. Non-adherence should be excluded.
Routinely collected questionnaires/ self-reports	Antidepressant treatment or treatment with (es)ketamine	Patient-reported medication history can be used if register data is incomplete.
	Treatment non-response/resistance	Self-reported non-response after ≥2 antidepressant trials.
	Side effects	Switches due to side effects should not be considered as non-response.
	Adherence	Adherence measured using patient reports should only be used when no other adherence measures such as drug concentrations from therapeutic drug monitoring are available. From TDM, non-detectable drug concentrations can be used as indicator of non-adherence. Non-adherence should be excluded.

MDD = major depressive disorder; TRD = treatment-resistant depression; BIP = bipolar disorder; ICD = International Classification of Diseases; ECT = electroconvulsive therapy; TMS = transcranial magnetic stimulation. ATC = anatomical therapeutic chemical. TDM = therapeutic drug monitoring.

Box 1: Recommendations for antidepressant treatment outcome definitions in major depressive disorder

Non-response/treatment-resistant depression:

- Diagnosis of major depression and
- Antidepressant switching (≥2 antidepressant trials of adequate dose and duration) and/or
- Hospitalization during treatment and/or
- Neurostimulation (electroconvulsive therapy or transcranial magnetic stimulation) and/or
- Treatment with (es)ketamine and/or
- Self-reported non-response after ≥2 antidepressant trials and
- Treatment adherence

Remission/response:

- Diagnosis of major depression and
- History of stable treatment and
- No history of neurostimulation (electroconvulsive therapy or transcranial magnetic stimulation) and
- No history of treatment with (es)ketamine and
- No hospitalization during treatment and/or
- Self-reported treatment response and
- Treatment adherence

Table 2: Recommendations for measuring treatment outcomes in schizophrenia using real-world data

RWD sources	**Phenotype**	**Criteria**
Population-wide health registries	Diagnosis	Diagnosis of SCZ is required and should be obtained from specialist health care alternatively from primary care (ICD10).
	Lifetime clozapine treatment	Medication use from prescription registry (ATC code N05AH02) or from clozapine registries.
	Antipsychotic switching	Medication use from prescription registry (ATC codes N05A): To define treatment resistance, it should be ≥2 antipsychotic switches, and each switch should between 6 weeks (for adequate treatment duration) and 14 weeks (to exclude treatment interruption) of the previous antipsychotic prescription.
	Stable treatment (as proxy for response)	Treatment for ≥6 months of the same antipsychotic.
	Adequate treatment duration	Obtained from prescription registry: Should be ≥6 weeks to reduce the risk of switches due to side effects.
	Adequate dose	Daily dose from prescription registry: Should have minimal dose recommended for SCZ.
	Hospitalization	Hospitalization due to SCZ; should be during antipsychotic treatment
	ECT	ECT should be during or shortly after antipsychotic treatment.
	Comorbidity	Other psychiatric diagnoses should be excluded if these are the main diagnosis.
	Adherence	Using prescription registry data, the ratio between prescribed and dispensed medication can be calculated to estimate adherence. From TDM, non-detectable drug concentrations can be used as indicator of non-adherence. Non-adherence should be excluded.
Routinely collected questionnaires/ self-reports	Lifetime clozapine treatment	Patient-reported medication history can be used if register data is incomplete.
	Treatment non-response/resistance	Self-reported non-response after ≥2 antipsychotic trials.
	Side effects	Switches due to side effects should not be considered as non-response.
	Adherence	Adherence measured using patient reports should only be used when no other adherence measures such as drug concentrations from therapeutic drug monitoring are available. Non-adherence should be excluded.

MDD = major depressive disorder; SCZ = schizophrenia; BIP = bipolar disorder; ICD = International Classification of Diseases; ATC = anatomical therapeutic chemical; ECT = Electroconvulsive therapy. TDM = therapeutic drug monitoring.

Box 2: Recommendations for antipsychotic treatment outcome definitions in schizophrenia

<u>Treatment-resistant schizophrenia</u>:

- Diagnosis of schizophrenia and
- Lifetime clozapine use and/or
- Antipsychotic switching (≥2 antipsychotic trials of adequate dose and duration) and/or
- Electroconvulsive therapy and/or
- Hospitalization during treatment and/or
- Self-reported non-response after ≥2 antipsychotic trials and
- Treatment adherence

<u>Non-resistance/Response:</u>

- Diagnosis of schizophrenia and
- No history of clozapine and
- No history of electroconvulsive therapy and
- History of stable treatment and
- No hospitalization during treatment and/or
- Self-reported treatment response and
- Treatment adherence

Table 3: Recommendations for measuring treatment outcomes in bipolar disorder using RWD

RWD sources	Phenotype	Criteria
Population-wide health registries	Diagnosis	Diagnosis of BIP is required and should be obtained from specialist health care, alternatively primary health care (ICD10).
	Bipolar treatment	Medication use from prescription registry: ATC code N05AN01 (lithium), N03A (antiepileptics), N05A (antipsychotics) and N06A (antidepressants), as well as ketamine (N01AX03) and esketamine (N01AX14).
	Polypharmacy	Non-response/resistance in maintenance treatment: Combined treatment with ≥3 medications to treat BIP (lithium, antiepileptics, antipsychotics, antidepressants). Non-response/resistance in mania: Combined treatment with ≥3 anti-manic drugs (lithium, antiepileptics, antipsychotics). Non-response/resistance in bipolar depression: ≥2 antidepressant treatments (antidepressants, mood stabilizers, ketamine) added to the maintenance treatment.
	Medication switching	Non-response/resistance in maintenance treatment: Should be ≥2 switches between different medications to treat BIP (lithium, antiepileptics, antipsychotics, antidepressants), regardless of monotherapy or combination therapy. Non-response/resistance in mania: Should be ≥2 switches between different medications to treat mania (lithium, antiepileptics, antipsychotics), regardless of monotherapy or combination therapy. Non-response/resistance in bipolar depression: Should be ≥2 switches between antidepressant treatments (antidepressants, mood stabilizers, ketamine), regardless of monotherapy or combination therapy.
	Lifetime clozapine treatment	Medication use from prescription registry: ATC code N05AH02.
	Stable treatment (maintenance)	Treatment for ≥6 months with 1-2 drugs to treat BIP (lithium, antiepileptics, antipsychotics, antidepressants).
	Adequate treatment duration	Obtained from prescription registry: Should be ≥6 weeks to reduce the risk of switches due to side effects.
	Adequate dose	Daily dose from prescription registry: Should have minimal dose recommended for BIP.
	Hospitalization	Hospitalization during acute mania (to identify manic episodes) or during major depressive episode (to identify depressive episodes) or during maintenance treatment for BIP (to identify treatment strategies that failed to prevent future episodes).
	Comorbidity	Other psychiatric diagnoses should be excluded if these are the main diagnosis.
	Functional outcomes	Functional outcomes such as employment.
	Neurostimulation (ECT or TMS)	Neurostimulation should be during or shortly after pharmacological treatment for BIP.
	(Es)ketamine treatment	Treatment with ketamine/esketamine should be during a depressive episode (to define non-response/resistance in bipolar depression).
	Adherence	Ratio between prescribed and dispensed medication can be calculated to estimate adherence. From TDM, non-detectable drug concentrations can be used as indicator of non-adherence. Non-adherence should be excluded.

Routinely collected questionnaires/ self-reports	Bipolar treatment	Patient-reported medication history can be used if register data is incomplete.
	Polypharmacy	Patient-reported history on combination treatment for BIP (lithium/mood stabilizers, antipsychotics, antidepressants) to define non-response/resistance in mania, depression, maintenance (same criteria as for registry data).
	Lifetime clozapine treatment	Patient-reported medication history can be used if register data is incomplete.
	Treatment non-response/resistance	Self-reported non-response after ≥2 trials of pharmacological treatment for BIP to define non-response/resistance in mania, depression, maintenance (same criteria as for registry data).
	Functional outcomes	Patient-reported information about functional outcomes such as employment.
	Side effects	Switches due to side effects should not be considered as non-response.
	Adherence	Adherence measured using patient reports should only be used when no other adherence measures such as drug concentrations from therapeutic drug monitoring are available. Non-adherence should be excluded.

BIP = bipolar disorder; ICD = International Classification of Diseases; ATC = anatomical therapeutic chemical; ECT = Electroconvulsive therapy; TMS = transcranial magnetic stimulation. TDM = therapeutic drug monitoring.

Box 3: Recommendations for treatment outcome definitions in bipolar disorder

Non-response/treatment-resistance:

- Diagnosis of bipolar disorder and
- Medication switching (≥2 trials of medications (different criteria for non-response/resistance during maintenance treatment, acute mania, or bipolar depression), of adequate dose and duration) and/or
- Hospitalization during treatment (maintenance, mania, or depression) and/or
- Neurostimulation (electroconvulsive therapy or transcranial magnetic stimulation) during treatment maintenance, mania, or depression) and/or
- Treatment with (es)ketamine and/or
- Clozapine treatment and/or
- Polypharmacy (combined treatment with ≥3 medications for maintenance treatment, treatment of acute mania, or treatment of bipolar depression) and/or
- Self-reported non-response after ≥2 trials of medications (for maintenance treatment, treatment of acute mania, or treatment of bipolar depression) and
- Treatment adherence

Non-resistance/response:

- Diagnosis of bipolar disorder and
- History of stable treatment and
- No history of clozapine and
- No history of neurostimulation (electroconvulsive therapy or transcranial magnetic stimulation) during mood stabilizer treatment and
- No hospitalization during treatment and/or
- Self-reported treatment response and
- Treatment adherence

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