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Shared Decision Making in Schizophrenia

Evidence assessment and development of a digital Decision Aid for antipsychotic side effects: PROTECTS-SE

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Table of contents

Introduction

Schizophrenia and burden of antipsychotics side effects on patients' quality of life, functioning and mortality

Schizophrenia is a debilitating, and often life-long disorder that ranks among the 20 top causes of disability according to the Global Burden of Disease Report (1). The psychopathology of the disorder is characterized by positive and negative symptoms. Positive symptoms are essentially amplifications or distortions of typical functions, including experiences like delusions, hallucinations, and disorganized thinking. On the other hand, negative symptoms are marked by a decrease or absence of behaviors and expressions that are usually present, such as lack of motivation, reduced pleasure in activities, social withdrawal, diminished emotional expression, and impaired speech (2).

The life morbid risk for schizophrenia is approximately 1% (mean/median 11/7 per 1000), the median point prevalence per 1000 is 4.6 (10, 90 percent quantiles 1.9, 10.0), and the median yearly incidence per 100.000 is 15.2 (10%-90% percentiles [7.7-43.0]) (3). Patients with schizophrenia have an increased risk of death more than doubled over the general population (RR=2.52, 95% CI: 2.38-2.68)(4). The most common reason of death in these patients is suicide (RR=9.76-8.42). However, multiple natural causes play a relevant role in increased mortality such pneumonia (RR=7.00, 95% CI: 6.79-7.23), decreasing through infectious or endocrine or respiratory or urogenital or diabetes causes (RR=3 to 4), to alcohol or gastrointestinal or renal or nervous system or cardio-cerebrovascular or all natural causes (RR=2 to 3), and liver or cerebrovascular, or breast or colon or pancreas or any cancer causes (RR=1.33 to 1.96)(5).

Schizophrenia's burden on patients, relatives and society is dramatic. According to the Global burden of disease report 2019 in terms of YLDs in the 15-49 age group (https://vizhub.healthdata.org/gbd-compare), schizophrenia ranks 9th in terms of years lived with disability (YLDs) globally (271.28 YLDs per 100.000). With estimated total costs of more than 29 billion Euro per year, schizophrenia is also among the most expensive illnesses in the EU.(6)

The core treatment in patients with schizophrenia are antipsychotics. These interventions are efficacious in the acute management of psychotic episodes and prevent their recurrence (7). However, these interventions are burdened by side effects that impacts on patients' quality of life and functioning. Some of the side effects are life threating in the short and in the long term (8). Moreover, these side effects, as a cause of patient discomfort, contribute to frequent patients' scarce medication adherence (9). This dramatically increase the relapse risk. Then, it is fundamental to ask patients about not only side effects emerging from current treatment, but also try to identify those side effects the patient would not tolerate at the moment of treatment initiation (10).

Guidelines recommendations for antipsychotics side effects management in schizophrenia

Guidelines play a pivotal role in the patients' clinical management. Relaying on well written guidelines not only provide a guarantee to patients to be treated with evidence-based approaches (11), but in Italy is also fundamental to cover the clinician from lawsuits from patients (12). Nevertheless, there are some aspects to consider when approaching a clinical guideline. There are some standards on the development on clinical guidelines and those are not always correctly applied (13). Internationally, the Appraisal of Guidelines for Research & Evaluation (AGREE-II) is a standard checklist to evaluate their quality (14). Moreover, in Germany, there are definitions based on the Association of Scientific Medical Societies in Germany (AWMF) model that differentiate the guidelines based on methodological rigor, dividing them into three levels (15): S1 (expert consensus), S2 (formal consensus and/or evidence-based), and S3 (comprehensive systematic evidence-based with formal consensus). Unfortunately, the topic of antipsychotics side effects management is not deepened in all guidelines. The number of schizophrenia guidelines with middle-high methodological rigor and presenting information about side effects is limited to British(16), Japanese(17), Scottish(18), American(19) and German(20) guidelines. These guidelines provide recommendations on the following side effects: sedation, orthostatic hypotension, tachycardia, glucose dysregulation and diabetes mellitus, hyperprolactinemia/sexual dysfunction, constipation, acute dystonia, akathisia, parkinsonism, tardive dyskinesia, increased salivation, weight gain, dry mouth, urinary incontinence, and tardive dystonia.

In addressing the side effect of sedation, the guidelines recommend a nuanced approach. Incorporating an adjunct like caffeine is suggested (19). Strategically timing the administration of the primary medication to coincide with the evening can align the sedative peak with the patient's sleep cycle, minimizing daytime drowsiness(19). Monitoring for pharmacological interactions (21), dose adjustments (19, 21), or ultimately, transitioning to an alternative medication (16, 18, 19, 21) are additional strategies to consider if sedation detrimentally impacts the patient's daily functioning.

For managing orthostatic hypotension, guidelines propose an integrative approach that includes the addition of salt/fluid-retaining corticosteroids as an adjunct therapy (19), while advising patients to adopt gradual positional changes, such as waking up slowly (19), to mitigate symptoms. Regular review of all medications for potential interactions is recommended (19), with particular attention to the adjustment of antihypertensive treatments. Dose reduction or a switch to an alternative therapy may also be considered if these measures do not suffice (19, 21).

In the context of tachycardia, the guidelines recommend considering an add-on therapy with a beta-receptor blocking agent to manage the heart rate (21). Additionally, evaluating current medications for interactions is crucial, with a specific emphasis on discontinuing any anticholinergic or stimulant medications that may contribute to an increased heart rate (19). If necessary, adjusting the dosage (19) or switching to an alternative medication (21) may also be viable strategies to address this side effect.

For addressing glucose dysregulation and diabetes mellitus, the guidelines suggest initiating diabetes treatment as part of a behavioral change strategy (19). Furthermore, they recommend further clinical investigation and consultation with a diabetologist to tailor a comprehensive treatment plan (19).

In managing hyperprolactinemia and associated sexual dysfunction, the guidelines recommend a multifaceted approach. Add-on therapies such as aripiprazole (21), bromocriptine (21), cabergoline (21), other dopamine agonists (19), and PDE-5 inhibitors (21) are suggested. Concurrently, it's important to check for drug interactions that may exacerbate the condition(19). Clinically, investigating other risk factors and measuring prolactin levels can provide further insight into treatment efficacy (21). If necessary, switching medications (16, 19, 21) or opting for a partial agonist may also be considered to mitigate these side effects (19).

To alleviate constipation, the guidelines suggest a combination of therapeutic strategies. These include add-on treatments with laxatives (19, 21) and stool softeners (19), as well as the use of enemas when necessary (19). Emphasis is also placed on behavioral modifications such as incorporating a fiber-rich diet and increasing physical activity to promote bowel movements (21). If

these interventions are insufficient, a medication switch could be considered (21).

To address acute dystonia, the guidelines recommend add-on therapy options such as anticholinergic agents (17, 21), antihistaminergic treatments (17), benztropine (19), and diphenhydramine (19). If these interventions are not effective, dose reduction (17, 19), stopping the causative medication (17), or switching to a different medication (17, 19) are also considered viable strategies.

In the management of akathisia, guidelines outline a protocol that includes add-on therapies such as benzodiazepines, mirtazapine, and beta-blockers to alleviate symptoms (19). Additionally, strategies like reducing the dose of the causative agent (17, 19, 21), stopping the medication (17), or switching to a second-generation antipsychotic (SGA) are recommended steps if initial therapies do not yield sufficient relief (17).

To manage parkinsonism as a side effect, the guidelines suggest add-on therapies such as amantadine (17, 19) and anticholinergic agents (16, 17, 19, 21). Dose reduction of the offending medication is also advised (17, 19, 21). If symptoms persist, stopping the medication (17) or switching to a second-generation antipsychotic (SGA) or a low-potency first-generation antipsychotic (FGA) may be necessary (17-19, 21).

For tardive dyskinesia, the guidelines recommend considering add-on therapy with a reversible inhibitor of the vesicular monoamine transporter (19). Other strategies include dose reduction of the causative agent (19) or stopping the medication altogether (16, 19). If these interventions are not effective, a switch to a second-generation antipsychotic (SGA) or a low-potency first-generation antipsychotic (FGA) may be explored (17, 18).

To manage increased salivation, the guidelines suggest various add-on therapies, including anticholinergic agents (19, 21), botulinum toxin (21), diphenhydramine (19), and alpha-blockers (19). Behavioral changes such as chewing sugarless gum to help with saliva swallowing and placing a towel on the pillow to manage nighttime salivation are also recommended (19). If these measures are insufficient, a switch to a different medication may be considered (21).

To address weight gain as a side effect, the guidelines recommend add-on therapy options, such as glucagon-like peptide-1 receptor agonists (19), metformin (18, 19, 21), and topiramate (19, 21), alongside psychosocial interventions (21). Behavioral changes, including adopting nutritional approaches, are also suggested (18, 19). It's important to check for interactions with other drugs that may induce weight gain (19). If these measures prove inadequate, switching to medications with a lower risk of weight gain, such as haloperidol, aripiprazole, or amisulpride, may be considered (18, 19, 21).

For the side effect of dry mouth, the guidelines suggest behavioral modifications such as increasing fluid intake (21) and using sugar-free drops or chewing gum (21). If these strategies do not provide sufficient relief, dose reduction or switching to a different medication may be necessary (21).

For urinary incontinence, the guidelines recommend add-on therapies such as carbachol and distigmine (21). Should these additional treatments be insufficient (21), dose reduction of the primary medication (21) or a switch to an alternative medication (21) may be considered.

For managing tardive dystonia, the guidelines indicate that dose reduction of the offending medication should be considered (17). If symptoms persist or are severe, stopping the medication may be necessary (17). Alternatively, a switch to another medication less likely to cause tardive dystonia could be explored (17).

Other indications are available for the following, less frequent side effects: orthostatic hypotension, constipation, increased salivation, neuroleptic malignant syndrome (NMS), QTc prolongation with higher grade arrhythmias, seizures, liver enzyme elevation, hyperlipidemia, various metabolic side effects, catatonia, sleep apnea syndrome, cardiomyopathy, myocarditis, cutaneous vasculitis, agranulocytosis, neutropenia, fever, and dermatological reactions.

As suggested, various side effects can be managed by reducing the dosage of medication. However, while this approach may seem intuitively effective, it isn't always the safest option, as it can lead to an increased risk of relapse (22) without necessarily reducing the side effects themselves (23). Therefore,

considering alternative approaches that are less risky and potentially more effective becomes crucial.

These alternatives could include switching to a different antipsychotic with a more favorable side-effect profile, augmenting with other medications to mitigate side effects, or implementing non-pharmacological interventions such as psychotherapy or lifestyle modifications. A personalized, holistic approach is key in managing schizophrenia, prioritizing both the control of symptoms and the overall well-being of the patient.

The relevance of patient reported outcomes in schizophrenia

Patient-reported outcome measures are data-driven metrics directly reported by patients (24). Their use is crucial in clinical practice as they allow for direct engagement with patients' experiences (24). In the last two decades, there has been an increase in the availability of these measurement tools (25). However, their implementation is still not widespread, despite the desirability of their broader dissemination (26). A critical step towards ensuring their widespread adoption involves identifying the best in terms of quality and effectiveness in meeting patient needs (27). Schizophrenia is associated with a significant burden on the quality of life (28), then it is crucial to include measures that truly represent the lived experiences of the patients themselves (29). This is particularly important in a healthcare system that should be oriented towards patient recovery. Incorporating such measures not only provides a more comprehensive understanding of the impact of these conditions but also aligns with a patient-centered approach to healthcare, facilitating more effective and empathetic treatment strategies(29).

In 2022, a consensus article was published in which over 100 professionals and service users defined which patient-reported outcomes to consider in monitoring patients with schizophrenia (30). Tests were identified for depressive symptoms and suicidal ideation, as well as other scales like the Modified Colorado Symptom Index for positive symptoms (31), and the Recovery Quality of Life (ReQoL-20) (32) for negative symptoms, quality of life, and the lived experience of Personal Recovery. Additionally, the WHO Disability Assessment Schedule 2.0 (WHO DAS 2.0) was highlighted for assessing global functioning (33).

Regarding the monitoring of side effects induced by antipsychotics, the identified tool is the 'Glasgow Antipsychotic Side-effect Scale' (GASS) (34). This hetero-administered instrument allows for the collection of information about side effects experienced in the last week, typically in about 5 minutes (35). The GASS was chosen due to its strong validity and reliability, making it suitable as a screening tool in current clinical practice (34). This scale's efficiency and effectiveness in quickly gathering pertinent data make it particularly valuable in busy clinical settings, ensuring that side effects are

consistently monitored and addressed in the treatment of patients on antipsychotic medication.

The opportunity of patients' involvement in shared decision making and their availability and utility of digital decision aids for schizophrenia

The Schizophrenia Commission has stated that "shared decision-making on medication choices is essential to improving outcomes [...]. This means practitioners discussing medication options fully with service users [and] providing them with quality information so that informed decisions can be made." (36)

Shared Decision Making (SDM) is defined as a collaborative process between patients and clinicians aimed at reaching a consensus on treatment modalities based on evidence and the values and preferences of patients (37). Traditionally, clinical practice often employed a paternalistic approach, where the patient had little to no say in clinical decisions (38). An intermediate phase was the informed consent approach, where the clinician made the decision and the patient agreed after being informed about the treatment strategy (38). In psychiatry, especially in the treatment of psychosis, the importance of implementing a non-coercive treatment approach is increasingly recognized, as it enhances outcomes and ensures optimization of patient empowerment (39). This shift signifies a more patient-centered approach, recognizing the patient's role as an active participant in their healthcare, thereby potentially improving compliance, satisfaction, and overall health outcomes (40).

In the context of schizophrenia, the management of patients primarily involves the use of antipsychotics initially (41). Research indicates that while these medications have similar efficacy levels, their tolerability profiles vary (42). Consequently, this variability allows for the consideration of patient preferences in clinical planning (43). This acknowledgment of patient preferences has spurred increased interest in 'decision aids', which have become more prevalent over the last decade, especially through digital tools (44). These aids support informed decision-making by providing patients with comprehensive information on treatment options, helping them to understand and weigh the benefits and side effects in line with their personal values and preferences (44). This approach aligns with the broader movement towards patient-centered care and shared decision-making in healthcare (45, 46).

As of today, several Shared Decision-Making tools are available in the psychiatric scientific literature, with some designed in digital format (44). These tools are aimed at presenting evidence-based data to facilitate the diagnostic and therapeutic process in patients with schizophrenia. The rise of these digital tools has led to the identification of the International Patient Decision Aid Standards (IPDAS), which are intended to guide researchers in the development of these instruments (47).

Elwyn and colleagues outlines the key aspects to consider in the development of patient decision aids (47). These include the presentation of probabilities, values, decision guidance, evidence development, disclosure, use of comprehensible language, and evaluation and testing of the device (47). This comprehensive framework ensures that the decision aids are not only informative but also accessible and user-friendly, supporting patients in making informed choices about their treatment in line with their personal values and circumstances.

Aim of the PhD thesis

The initial goal of this doctoral project was to create a Digital Decision Aid specifically designed to support clinicians in the process of antipsychotic dose reduction. To this end, a dual Cochrane review was planned to gather evidence on the efficacy and tolerability of reducing the dose of antipsychotics (23), and for transitioning from polypharmacy to monotherapy (48). However, the outcomes of these reviews and recent literature (22) discouraged a sole focus on dose reduction and redirected the project towards creating a Digital Decision Aid for managing side effects according to guidelines, where dose reduction becomes one of several treatment options. In order to create this tool, it was necessary to translate the gold standard of Patient Reported Outcomes in terms of collecting information about the side effects of antipsychotics, namely the Glasgow Antipsychotics Side Effect Scale (49), which was then incorporated into the final tool.

This approach ensured a comprehensive and evidence-based framework for clinicians to make informed decisions about managing side effects in schizophrenia treatment. By incorporating various treatment options and aligning with high-quality guidelines (16-19, 21), the tool aimed to optimize patient outcomes while minimizing risks. The focus on a user-friendly digital format also reflects the growing trend towards incorporating technology in healthcare decision-making processes, enhancing accessibility and efficiency.

Evidence Synthesis

Antipsychotic dose reduction compared to dose continuation for people with schizophrenia

The ensuing section provides a detailed summary of the publication cited below:

Rodolico, A., Siafis, S., Bighelli, I., Samara, M. T., Hansen, W. P., Salomone, S., Aguglia, E., Cutrufelli, P., Bauer, I., Baeckers, L., & Leucht, S. (2022). Antipsychotic dose reduction compared to dose continuation for people with schizophrenia. *The Cochrane database of systematic reviews*, *11*(11), CD014384. https://doi.org/10.1002/14651858.CD014384.pub2

Background

Antipsychotic medications are effective for managing acute schizophrenia and preventing relapse (50, 51), but they carry significant side effects like movement disorders and metabolic issues (3). There is controversy over whether high doses of antipsychotics might lead to brain volume loss (52). Clinically, high doses or combinations of antipsychotics are common due to factors like suicide risk, aggressive behavior, need for short hospital stays, and high non-response rates(53, 54). A systematic review found that 20% of schizophrenia patients received polypharmacy, and 10% were on doses above recommended levels (55, 56). Clinicians must decide if high-dose antipsychotics can be reduced after the acute phase without compromising relapse prevention. However, there's a risk of relapse with dose reduction or discontinuation, which poses a difficult trade-off (50). Our review focuses on randomized controlled trials that assess the impact of antipsychotic dose reduction versus continuation of the same dose.

Description of the condition

Schizophrenia is a chronic and debilitating mental disorder affecting about 1% of the global population (4, 57), typically emerging in early adulthood with severe symptoms (58). It presents with 'positive' symptoms like delusions and hallucinations, 'negative' symptoms such as apathy and lack of motivation, disorganized behavior and thought, and catatonic symptoms including unusual mannerisms and posturing (58). As a leading cause of long-term disability, schizophrenia has profound effects on patients and their families, with reduced employment rates ranging from 4.5% to 50% and a lifetime suicide prevalence of 4% to 10%, particularly among males early in the disorder's course (59-63). The quality of life is often poor and tends to worsen over time, with an average reduction in lifespan of about 15 years (3).

The illness progresses through three stages: the prodromal phase with initial behavioral, emotional, and cognitive changes; the acute phase with pronounced psychotic symptoms; and the remission phase where symptoms subside but maintenance treatment is usually necessary to prevent relapses (51, 64). Remission is a step towards recovery, defined as the ability to function socially and vocationally in the community and being relatively free of disease-related psychopathology (64).

Description of the intervention

Antipsychotic medications are essential in treating schizophrenia, with long-term administration typically necessary to avert relapse risks (51). Despite their importance, these drugs are associated with numerous adverse effects, such as movement disorders, weight gain, metabolic issues, sexual dysfunction (50), potential brain volume reduction (52), and heightened mortality risk (4) which are often correlated with dosage (65, 66). Therefore, a gradual reduction in dosage could significantly enhance patient well-being (65). However, the risk of relapse becomes pronounced if the dosage is too low. The strategy of dose reduction involves decreasing the initial antipsychotic dose by varying amounts, with specific methods differing (67). Reductions might be a fixed percentage (68) or a slow tapering towards complete cessation, with the option to restart and adjust the medication if symptoms recur (69). Reducing the number of antipsychotics in polypharmacy is also a form of dose reduction (70). The extent to which doses can be safely reduced is uncertain due to individual differences in drug metabolism and genetic factors (71) , and the optimal pace for dose reduction in schizophrenia patients is not well-defined (67).

How the intervention might work

The rationale for reducing antipsychotic dosage is based on the understanding that many adverse effects are dose-dependent, including serious somatic events (66), weight gain (72), QT prolongation (73), and tardive dyskinesia (74). Antipsychotics primarily work by blocking dopamine D2 receptors, with 60% to 80% occupancy needed for efficacy, which is dose-related (75). Higher doses increase receptor occupancy and the risk of extrapyramidal side effects. Similar correlations are presumed for other receptors, like histamine H1 receptors causing sedation or muscarinic receptors leading to

anticholinergic effects (65). Reducing the antipsychotic dose should therefore reduce the adverse-effect burden (76-79). Adverse effects can diminish quality of life and hinder community functioning (43, 80). A study suggested improved functional outcomes in first-episode schizophrenia patients who underwent dose reduction compared to those who continued with higher doses (69). Additionally, high doses have been linked to brain volume loss, a contested finding (52, 81), but if accurate, dose reduction might mitigate this issue. The primary risk of dose reduction is the potential reemergence of psychotic symptoms, which can lead to rehospitalization and negatively impact personal and vocational life (51).

Why it is important to do this review

There is ongoing debate about whether individuals with schizophrenia are prescribed higher antipsychotic doses than necessary. Concerns stem from studies suggesting a dose-related brain volume loss associated with long-term antipsychotic use (52), though these findings are contentious (81) and their clinical significance remains uncertain (82). Distinguishing between volume changes caused by medication and those resulting from the illness itself is challenging (83). Long-term studies indicate that up to 20% of first-episode schizophrenia patients may not have a second episode (84, 85). Some epidemiological evidence suggests that untreated schizophrenia patients fare better overall (86), while other research from rural China indicates higher mortality among untreated individuals compared to those receiving treatment (87). Identifying patients who could benefit from reduced medication in advance is not currently possible. Given the complexity and potential implications for treatment guidelines and policy, due to the high societal costs of schizophrenia (88), a systematic review of the data is crucial.

Objectives

The objectives are to evaluate the effects and safety of reducing antipsychotic doses versus maintaining current doses for individuals with schizophrenia, and to investigate the factors influencing dose reduction, including the extent and speed of such reductions.

Methods

Criteria for considering studies for this review

Types of studies

For this review, we included all relevant randomized controlled trials (RCTs). Trials described as 'double-blind' with implied randomization were also considered, with their impact assessed through sensitivity analysis. If including these trials did not significantly alter results, they remained in the analyses. However, if their inclusion led to clinically significant differences, we presented their data separately and did not combine them with higher-quality trial results.

Quasi-RCTs, such as those using alternate days for allocation, were excluded. For studies with multiple reports, we consolidated them into a single entry.

Types of participants

Participants included adults diagnosed with schizophrenia or related disorders, such as schizophreniform disorder, schizoaffective disorder, and delusional disorder, regardless of the diagnostic criteria used. We considered participants stabilized on their current antipsychotic treatment, without restrictions on age, gender, race, or country. Stability definitions were taken as per the individual studies. Studies focusing on the minimum effective dose for acutely ill patients were excluded. We aimed to ensure the review's relevance to current schizophrenia care by clearly highlighting the clinical state (early post-acute, partial remission, remission), illness stage (first episode, early illness, persistent), and any focus on specific issues (e.g., negative symptoms, treatment-resistant illnesses).

Types of interventions

1. Dose reduction

We considered any reduction in the dose of a current antipsychotic drug that is licensed in at least one country, regardless of the definition of reduction or the speed at which it was implemented. Studies included in the review allowed for a gradual reduction in antipsychotic dosage, up to and including complete withdrawal, provided there was an option to increase the dose again if symptoms returned. We excluded studies that involved complete withdrawal of antipsychotics for all participants without the option of dose escalation if needed, as the focus of this review was on the effects of dose reduction rather than complete withdrawal. Additionally, studies on 'intermittent treatment', where medication is abruptly stopped and only resumed upon signs of psychosis, were also excluded. We intended to explore

the extent of dose reduction in a subgroup analysis to better understand its impact.

2. Dose continuation

Continuation of the current antipsychotic dose.

Types of outcome measures

Outcomes in the review were categorized based on duration into very short term (up to three months), short term (up to six months), medium term (up to one year, i.e., seven to 12 months), and long term (more than 12 months). The primary focus was on outcomes within the first year. When data for separate time points were available, we reported them individually and calculated subtotals without generating overall totals, to prevent double counting in cases where a single study provided data for multiple time points. In instances where multiple time points from the same study were reported, we chose the data point closest to 12 months for the primary analysis to maintain consistency and relevance to the medium-term outcomes of interest.

Primary outcomes

1 **Quality of Life:**

- Clinically important change in quality of life, as defined in each study.

2 **Service Use:**

- Hospital readmission rates.

3 **Adverse Effects:**

- Number of participants leaving the study early due to adverse effects, indicating overall tolerability.

Secondary Outcomes:

1 **Quality of Life:**

- Mean endpoint or change score on any published quality of life scale.

2 **Service Use**

3 **Functioning:**

- Clinically important change in functioning, as defined in each study.
- Mean endpoint or change score on any published functioning scale.

4 **Global State:**

- Relapse or exacerbation of psychosis, as defined by the original authors.

◦ Mean endpoint or change score on any published global state scale.

5 Study Discontinuation:

◦ Number of participants leaving the study early for any reason, indicating overall acceptability.

◦ Number of participants leaving the study early due to inefficacy, indicating overall efficacy.

6 Mental State:

◦ Clinically important change in general mental state, as defined by the individual studies.

◦ Mean endpoint or change score on general mental state scale.

◦ Clinically important change in positive symptoms, and mean endpoint or change score on a positive symptom scale.

◦ Clinically important change in negative symptoms, and mean endpoint or change score on a negative symptom scale.

◦ Clinically important change in depressive symptoms, and mean endpoint or change score on a depressive symptom scale.

7 Behavior:

◦ Mean endpoint or change score on any published behavior scale.

8 Satisfaction with Care:

◦ Mean endpoint or change score on any published satisfaction with care scale.

9 Adverse Effects/Events:

◦ Incidence of at least one adverse effect.

◦ Clinically important change in weight gain.

◦ Incidence of various specific adverse effects.

◦ Mortality rates, including overall mortality, mortality due to natural causes, and mortality due to suicide.

10 Medication:

◦ Mean antipsychotic dose at the study endpoint.

The review employed a range of scales and criteria from the original studies to assess outcomes, providing a thorough analysis of the impact and safety of reducing antipsychotic doses in schizophrenia patients. To standardize the measurement of medication doses, we converted antipsychotic dosages to

olanzapine equivalents (89). In cases where a drug was not included in the Gardner conversion, we used defined daily doses (DDDs) as an alternative method (90).

Search methods for identification of studies

The Cochrane Schizophrenia Group's Study-Based Register of Trials was searched on February 10, 2021, using the term **Dosage Reduction** in the intervention field of the study. This register, organized by interventions and linked to relevant topics, enables efficient and precise retrieval of studies (91-93), minimizing waste in systematic review processes (94). The register is maintained through systematic searches of major databases, including CENTRAL, MEDLINE, Embase, CINAHL, PsycINFO, PubMed, ClinicalTrials.gov, ISRCTN registry, WHO ICTRP, as well as ProQuest Dissertations and Theses A&I, handsearches, grey literature, and conference proceedings, without restrictions on language, date, document type, or publication status (95). Additional resources were searched by inspecting references from included studies, previous reviews, and guidelines. Personal contacts were made with the first authors of included studies for additional data. Pharmaceutical companies of second-generation antipsychotics were also contacted for further studies when indicated by the literature search.

Data collection and analysis

After removing duplicates, at least two review authors (IBi, AR, LB, IBa, SS, PC) independently screened citations and identified relevant abstracts using Covidence. Disputes were resolved by acquiring full reports for closer examination. The same review authors independently reviewed full reports that met the inclusion criteria, with any disagreements settled through discussion with another author (SL) or by contacting the study authors for clarification.

For data extraction, two authors independently gathered data from the included studies, resolving discrepancies through discussion or by reaching out to study authors for missing information or clarification. Data from graphs

and figures were included only if two authors independently agreed on the results.

Extracted study characteristics included methods, participants, interventions, outcomes, sponsorship, country, and trial registration ID. Data were managed using Covidence software after testing the process with a sample of five studies.

For the review, continuous data from rating scales were included only if the scale's psychometric properties had been peer-reviewed (96), the scale was not modified by the trialists for the specific trial.

The review primarily used endpoint data over change data due to the challenges of obtaining two assessments in conditions like schizophrenia. However, change data were used if endpoint data were unavailable or if substantial baseline imbalances could influence the results.

Skewed data were handled carefully, with specific standards applied to ensure appropriate analysis (97).

Continuous data were converted to a common metric for comparison across trials, and continuous outcomes were also converted to binary data when possible, using a 50% reduction in scale scores as a threshold for clinical improvement (98, 99) or the primary cutoff provided by original study authors.

Forest plots were oriented so that the left of the line of no effect indicated a favorable outcome for dose reduction, except when avoiding awkward double negatives in titles, in which case the orientation was reversed and noted accordingly.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias for included studies using the RoB 2 tool (100), following criteria from the Cochrane Handbook for Systematic Reviews of Interventions(101). They evaluated bias across five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of reported results. Judgments were made (high risk, some concerns, low risk) using the RoB 2 tool's algorithms.

The focus was on the effect of assignment to interventions at baseline (intention-to-treat effect). The tool was applied to outcomes including quality of life, hospital readmission, adverse effects and tolerability, functioning, global state, study discontinuation, and adverse events.

For cluster-randomized trials, an additional domain specific to such trials was used, and for cross-over trials, only data from the first phase were considered. Disagreements were resolved by consensus with another author (SL), and attempts were made to contact study authors for missing information. The risk of bias was reported in the review text, in tables, and next to forest plots for outcomes contributing to the summary of findings.

If predefined outcomes were unavailable but similar data were present, the risk of bias for these proxy outcomes was also rated.

Measures of treatment effect

For binary outcomes, the review calculated risk ratios (RR) and their 95% confidence intervals (CI) due to their intuitive nature and because clinicians often misinterpret odds ratios as RRs (102, 103). While the number needed to treat for an additional beneficial outcome (NNTB) and harmful outcome (NNTH) are appealing, they are challenging to calculate and interpret in meta-analyses (104). Instead, illustrative comparative risks were provided in the summary of findings table when feasible.

For continuous outcomes, mean differences (MDs) with 95% CIs were calculated when studies used similar scales for a given outcome. If scales varied significantly, standardized mean differences (SMDs) were estimated to measure the effect size between groups.

Unit of analysis issues

Cluster randomization (e.g., by clinician or practice) is common but poses analytical challenges, often leading to unit of analysis errors with overly narrow CIs and inflated statistical significance (105-107).

When clustering was considered in the primary studies, data were adjusted for the clustering effect. Efforts were made to obtain intraclass correlation coefficients (ICCs) to adjust results using the design effect formula: design effect = $1 + (m - 1) \times ICC$ (108) , assuming an ICC of 0.1 if not reported

(109). Properly analyzed cluster studies with accounted ICCs could be synthesized with other studies using the generic inverse-variance method.
Carry-over effects are a significant concern in cross-over trials, where effects from the first phase may influence the second phase, especially in severe mental illness. Therefore, only data from the first phase of cross-over studies were used.
For studies with more than two treatment arms, additional arms were included in the analysis if relevant. Binary data from multiple arms were added to the 2 x 2 tables, while continuous data were combined using the formula from the Cochrane Handbook (101). Treatment arms not relevant to the analysis were not reported.

Dealing with missing data

The reviewers acknowledges concerns regarding the credibility of data when there is a significant degree of loss to follow-up (110). However, due to the lack of clarity on when attrition becomes problematic, studies were not excluded based on attrition levels. Instead, attrition was considered in the risk of bias assessment. For binary outcomes, data were presented using an intention-to-treat (ITT) analysis, with the post hoc assumption that participants who left the study early did not experience the outcome. This conservative approach is commonly employed in meta-analyses of antipsychotics for schizophrenia to avoid overestimating risk (111). To address participants who leave trials early or are lost to follow-up, various methods are used, including last observation carried forward (LOCF), multiple imputation, and mixed-effects models for repeated measurements (MMRM). Studies were not excluded based on the statistical method employed, but preference was given to more sophisticated approaches like MMRM or multiple imputation over LOCF. Completer analyses were used only when ITT data were unavailable, and studies with only completer data were excluded in a sensitivity analysis. For missing standard deviations (SDs), attempts were made to contact authors. If SDs were still unavailable, they were calculated from standard errors (SE), confidence intervals (CIs), P values, t values, or other statistics using formulas from the Cochrane

Handbook (101). If these methods were inapplicable, SDs were imputed using other included studies' SDs (112). Although imputation can introduce errors, excluding studies would result in loss of data. The validity of imputed values was assessed in a sensitivity analysis that omitted these values.

Assessment of heterogeneity

The review assessed clinical heterogeneity by initially considering all included studies to identify any outlier participants or unexpected situations for discussion. Methodological heterogeneity was similarly evaluated, with a focus on identifying and discussing any outlying methods not anticipated in the study design. For statistical heterogeneity, visual inspection of graphs and the I^2 statistic alongside the Chi^2 P value were used to estimate the percentage of inconsistency due to chance (113). Substantial heterogeneity was indicated by an I^2 statistic of 50% or greater with a significant Chi^2 statistic, prompting further investigation through subgroup analysis (101). Regarding reporting biases, which are influenced by the nature and direction of research findings (114), the authors was cautious in using funnel plots due to their limited power in detecting small-study effects. Funnel plots were employed for outcomes with a sufficient number of studies and variation in size, and contour-enhanced funnel plots were created with statistical guidance for interpretation (115). These analyses aimed to explore potential biases in the reporting of research findings.

Data synthesis

The authors acknowledges the ongoing debate regarding the preference for fixed-effect or random-effects models. The random-effects approach assumes that different studies estimate varying but related effects, which often seems to be the case. This model accounts for differences between studies even in the absence of statistically significant heterogeneity. However, a notable drawback of the random-effects model is that it gives more weight to smaller studies, which may be more prone to bias, potentially leading to overestimation or underestimation of the effect size. Despite this, the review

opted to use a random-effects model for all analyses to accommodate the variability among the included studies.

Subgroup analysis and investigation of heterogeneity

The reviewers conducted subgroup analyses on primary outcomes to explore the effects of various moderators. However, the review authors recognize that these analyses are exploratory. For continuous moderators, meta-regression was used when there were sufficient studies. The degree of dose reduction was analyzed, with doses converted to olanzapine equivalents to assess the impact on primary outcomes. The speed of dose reduction was categorized to examine its influence on relapse rates, with a particular focus on abrupt versus gradual reduction.

Initial antipsychotic doses were considered, hypothesizing that starting doses might influence outcomes, and severity of illness was also examined, with the suggestion that dose reduction could be more feasible in less severe schizophrenia. Subgroups based on clinical state, stage, or specific conditions, such as first-episode patients or those in remission, were analyzed to determine the pertinence of dose reduction in these populations.

Additionally, a post hoc analysis looked at the endpoint antipsychotic dose in the dose reduction group to investigate the relationship between relapse and the mean dose at the endpoint, using olanzapine equivalents and estimating doses before any relapse.

In terms of heterogeneity, the reviewers reported inconsistency and verified data accuracy. Outlying studies were visually inspected and potentially removed to determine their impact on homogeneity. Decisions to exclude studies or avoid meta-analysis were based on the nature of heterogeneity. When unexpected clinical or methodological heterogeneity was found, hypotheses were stated for consideration in future reviews or updates, rather than conducting further analyses.

Sensitivity analysis

The authors planned sensitivity analyses for primary outcomes to assess the impact of specific factors by excluding studies identified for each analysis and comparing the results with the main analysis.

The effects of excluding trials at high risk of bias were examined to see how they influenced the primary outcomes. The impact of removing data from trials with imputed values for intraclass correlation coefficients (ICCs) in cluster RCTs or imputed standard deviations (SDs) was also analyzed.

Trials that did not use operational criteria to diagnose schizophrenia were considered for exclusion to evaluate their effect on the results. Although a random-effects model was used in the main analyses, a fixed-effect model was applied in a sensitivity analysis to determine if there was a significant change in the results for the primary outcomes.

The reviewers looked at the effects of excluding data from trials with potential skewness in the data (mean/SD ratio < 2). If this exclusion altered the results significantly, these studies were also removed from the main analysis and presented separately.

Additionally, studies from mainland China were considered for exclusion due to potential differences in randomization methods, brevity of reports, and lack of detailed method descriptions, which could affect the robustness of the findings.

Summary of findings and assessment of the certainty of the evidence

The review utilized the GRADE approach to interpret findings, which involved using GRADEpro GDT (116) software to import data from Review Manager Web (117) and create a summary of findings table. This table was designed to provide outcome-specific information on the overall certainty of evidence, the magnitude of the effects of the interventions, and the sum of available data on outcomes deemed important for patient care and decision-making. The overall judgments from the RoB 2 assessment were incorporated into the GRADE assessment.

The main outcomes intended for inclusion in the summary of findings table were quality of life (clinically important change), service use (readmission to hospital), adverse effects (leaving the study early due to adverse events),

functioning (clinically important change), global state (relapse/exacerbations of psychosis), study discontinuation (for any reason), and adverse effects/events (at least one adverse effect).

If data for a predefined outcome were unavailable but available for a similar outcome, the similar outcome was rated as a proxy for the predefined one.

Results

Summary of findings table

Outcome	*Dose Continuation*	*Dose Reduction*	*Relative Effect (95% CI)*	*Total Participants*	*Certainty of Evidence*
Quality of Life	-	-	-	719	Moderate
Hospital Readmission	82 per 1000	125 per 1000	RR 1.53 (0.84 to 2.81)	1433	Very Low
Study Dropouts (Adverse)	38 per 1000	83 per 1000	RR 2.20 (1.39 to 3.49)	1340	Moderate
Functioning	-	-	-	966	High
Psychosis Relapse	109 per 1000	236 per 1000	RR 2.16 (1.52 to 3.06)	2481	Low
Study Dropouts (Any Reason)	239 per 1000	330 per 1000	RR 1.38 (1.05 to 1.81)	1551	Moderate
Side Effects	598 per 1000	616 per 1000	RR 1.03 (0.94 to 1.12)	998	Moderate

Table A1. Summary of findings table

Description of included studies

The Cochrane Schizophrenia Group's Study-Based Register of Trials, complemented by handsearching, yielded 57 studies for detailed evaluation, culminating in 25 studies being incorporated into the review, with 22 contributing to the meta-analysis, involving a total of 2721 participants.

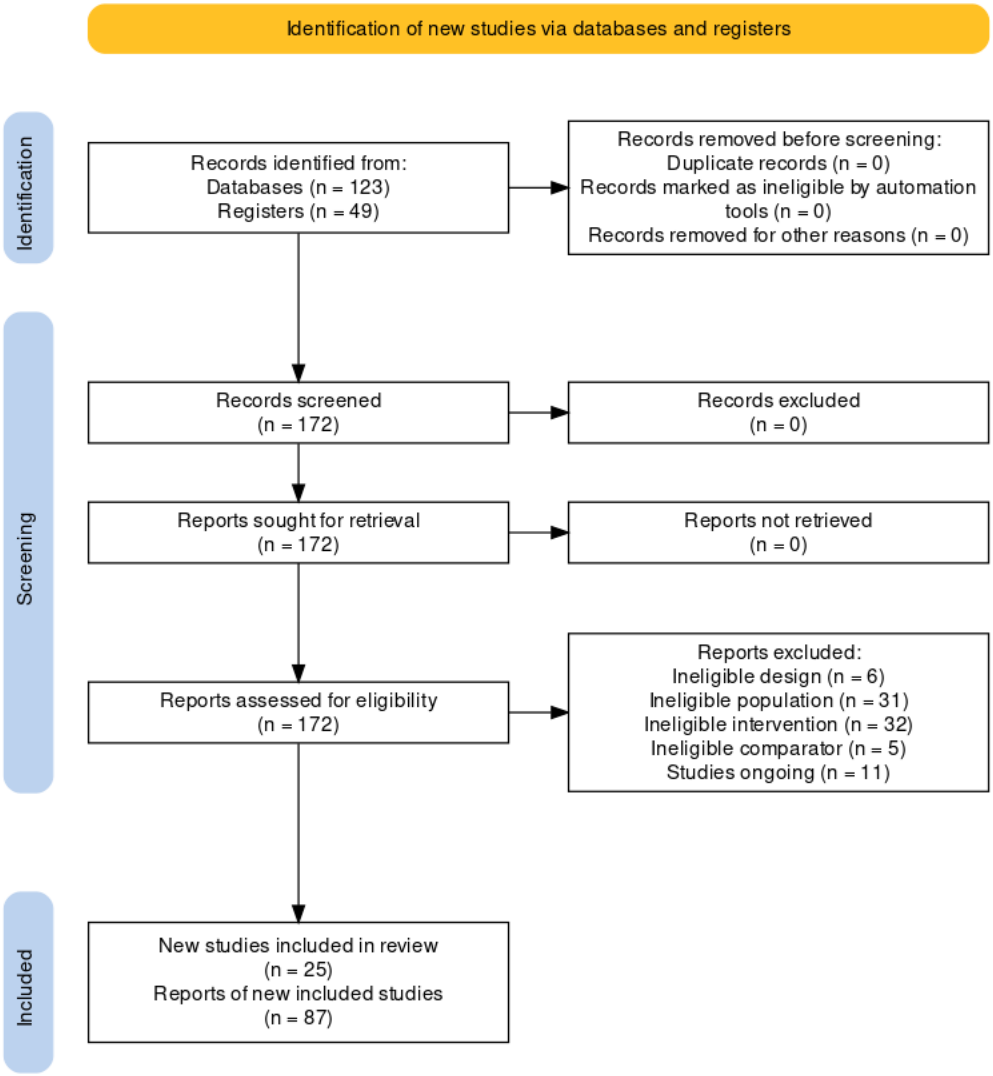

Figure A1. Prima flowchart

These studies, all randomized controlled trials (RCTs), varied in length, with durations ranging from 12 weeks to two years. Diagnostic criteria for schizophrenia among the studies included a range of classifications, from DSM-5 to Feighner criteria, and ICD-10 to Research Diagnostic Criteria. The studies predominantly featured participants in remission or partial remission, with some focusing on those with chronic illness. The median participant age was approximately 38.4 years, and study sizes varied, with the smallest including 18 participants and the largest encompassing 466.

Recruitment settings spanned inpatient, outpatient, and combined environments, with research conducted in diverse locations such as the USA, Canada, the UK, Europe, and Asia. Some studies were multicenter, involving participants from various countries. The interventions compared the

continuation of antipsychotics at the initial dose against a reduction regimen, which was either gradual or abrupt, with some aiming for complete withdrawal. The median target for dose reduction was 66%.

Outcomes were assessed using a variety of scales, and due to instances of incomplete reporting, authors were contacted for additional data and clarifications.

Included studies are described in Table A2.

Study name and year	*Country*	*Clinical state*	*Drug used*	*Dose reduction strategy*	*Dose reduction degree*	*Duration*	*Number of participants*	*Average age of participant*
Branchey 1981	USA	Chronically ill	Loxapine	Gradual	100%	36 weeks	33	51.7 years
Caffey 1964	USA	Chronically ill	Chlorpromazine or thioridazine	Abrupt	57.1%	16 weeks	177 (excluding placebo groups)	No information
Carpenter 1999	USA	Remission	Fluphenazine	Abrupt	67%	54 weeks	50	35.5 years
Cookson 1987	UK	Hebephrenic or paranoid schizophrenia	Cis(Z)-flupentixol	Abrupt	50%	44 weeks	18	44.5 years
Faraone 1989	USA	Chronically ill	Not specified	Gradual	80%	26 weeks	36	No information
Fleischhacker 2014	Multinational (14 countries)	Partial remission	Aripiprazole	Abrupt	94%	38 weeks	397 (total sample size 662 with all study arms)	40.9 years
Hirschowitz 1995	USA	Chronically ill	Haloperidol	No information	No information	5 weeks	32	No information
Hogarty 1988	USA	Partial remission	Fluphenazine decanoate	Flexible	80% at randomisation	104 weeks	70	28.3 years
Hogarty 1995	USA	Chronically ill	Fluphenazine decanoate	Abrupt	Not available	12 weeks	79	No information
Huhn 2020	Germany	Remission	Aripiprazole, olanzapine, perazine, quetiapine, risperidone	Gradual	Up to 100%	26 weeks	20	45.3 years
Johnson 1987	UK	Schizophrenia, remission	Flupenthixol decanoate	Abrupt	50%	52 weeks	60	40.9 years
Kane 1983	USA	Partial remission	Fluphenazine decanoate	Abrupt	Up to 90%	52 weeks	126	28.9 years
Kane 2010	Multinational (26 countries)	Partial remission	Olanzapine	Abrupt	Up to 92%	24 weeks	466 (total sample size 1065 with all study arms)	39.1 years
Kinion 2000	USA	Chronically ill	Not specified	Gradual	Not specified	26 weeks	27	73 years
Lonowski 1978	USA	Chronically ill	Thioridazine, chlorpromazine, haloperidol	Abrupt	87.5% (maximal dose reduction)	15 weeks	59	47.1 years
Newcomer 1992	USA	Remission	Haloperidol	Abrupt	50%	4 weeks	27	38.96 years
Ozawa 2019	Japan	Partial remission	Risperidone or olanzapine	Gradual	Reduction up to 65% dopamine D2	52 weeks	35	63.9 years

					receptor occupancy			
Remington 2011	Canada	Not specified	Loxapine, olanzapine, risperidone	Abrupt	50%	26 weeks	35	37.1 years
Rouillon 2008	France	Partial remission	Olanzapine and others not specified	Gradual	Up to 50%	26 weeks	97	39.4 years
Schooler 1997	USA	Partial remission	Fluphenazine decanoate and oral fluphenazine	Abrupt	80%	104 weeks	213	Not specified
Takeuchi 2014	Japan	Remission	Olanzapine, Risperidone	Gradual	Up to 50%	Up to 50%	61	39.7 years
Volavka 2000	USA	Chronically ill	Haloperidol	Gradual	33%	28 weeks	23	40.1 years
Wang 2010	China	Partial remission	Risperidone	Gradual	50%	4-week group: 56 weeks total (4 weeks + 52 weeks follow-up); 26-week group: 78 weeks total (26 weeks + 52 weeks follow-up)	374	32.6 years
Wunderink 2007	The Netherlands	Remission	Various (including risperidone, olanzapine, quetiapine, clozapine, zuclopenthixol)	Gradual	Up to 100%		131	Not specified
Zhou 2018	China	Partial remission	Olanzapine, Risperidone	Gradual	50%	52 weeks	75	Mean 44.6

Table A2. Included studies

Outcomes

The review employed a diverse array of scales to evaluate symptoms and adverse events. For quality of life, the EuroQol-5 Dimensions three-level version (EQ-5D-3L) (118) was used in one study (119) , while the Heinrich-Carpenter Quality of Life Scale (QLS) (120) was utilized in two studies (Carpenter 1999; Kane 2010). The Schizophrenia Quality of Life (S-QoL) (121) and the World Health Organization Quality of Life abbreviated form (WHOQOL-BREF) (122) were each used in one study (123, 124), respectively. The Subjective Well-Being Under Neuroleptic Treatment Scale (SWNS) (125) was employed in two studies (119, 126). The Global Assessment of Functioning (GAF) (127) in one study (128). The Groningen Social Disabilities Schedule (GSDS) (129) in another (124), and the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) (130) in one study (131). The Personal and Social Performance Scale (PSP) (132) was used in two studies (126, 133)), and the Strauss and Carpenter Level of Functioning Scale (SCLoF) (134-136) in one study (137).

Global state was measured with the Clinical Global Impression (CGI) (138), used in six studies for CGI-Severity (119, 126, 131, 133, 139), and in three for CGI-Improvement (126, 131, 133). The CGI scales for schizophrenia (CGI-SCH) (140) were used in one study (128). The Investigator's Assessment Questionnaire (IAQ) (141) was used in one study. The Symptom Checklist 90 (SCL-90) (142) was used in one study (143).

Mental state was evaluated using the Brief Psychiatric Rating Scale (BPRS)(144) in three studies (131, 137, 139) and Positive and Negative Symptom Scale (PANSS) (145) in ten studies (119, 123, 124, 126, 128, 131, 133, 146-148). The Negative Symptom Assessment 16 (149) and the Calgary Depression Scale for Schizophrenia (CDSS) (150) were each used in one study (119, 148), respectively. The Profile of Mood States Short Form (POMS-SF) (151) and the Schedule for Assessment of Insight (SAI) were also used in one study (119).

Satisfaction with care was assessed using the Medication Adherence Questionnaire (MAQ) (152) in one study (133), the Drug Attitude Inventory

(DAI) (153) in two studies (original (133), and short version (119)), and the Medication Adherence Rating Scale (MARS) (154), in one study (126). The Patient Satisfaction with Medication Questionnaire (PSMQ) (155) was used in one study (133).

Adverse effects were measured using the Udvalg for Kliniske Undersogelser (UKU) (156) in one study (126), the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) (157) in one study (124), and the Simpson and Angus Scale (SAS) (158) in seven studies (123, 128, 131, 133, 146-148). The Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) (159) and the Maryland Psychiatric Research Center Involuntary Movement Scale (MPRC) (160) were each used in one study (119, 137). The Barnes Akathisia Rating Scale (BARS) (161) was reported in three studies (128, 131, 133), and the Abnormal Involuntary Movement Scale (AIMS) (138) in seven studies (123, 126, 128, 131, 133, 139, 162). The Rockland Tardive Dyskinesia Rating Scale (RTDRS) (163) was used in one study (164), and the Columbia Suicide Severity Rating Scale (C-SSRS) (165) and the Clinical Global Impression - Severity of Suicidality (CGI-SS) (166) were each used in one study (133).

Cognition was measured with the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) (167, 168) in one study (148), and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) in one study (119)

Funding sources

The review's funding sources were diverse, with five studies sponsored by the industry, 14 studies publicly funded, two studies receiving joint funding from public institutions and pharmaceutical companies, and four studies lacking clear funding information.

Excluded studies

A total of 56 studies were excluded after full-text assessment for reasons such as non-randomized design, ineligible population (either not having schizophrenia or not being stable patients), interventions not involving dose

reduction, or comparators not involving dose maintenance. Six ongoing studies were identified that matched the inclusion criteria. There were no studies awaiting classification.

Risk of bias

The risk of bias across included studies was predominantly assessed as having some concerns. Most studies described participant allocation as randomized but lacked details on the random sequence generation. Only two studies showed potential issues with the randomization process due to baseline differences. Seven out of the 22 studies in the meta-analyses were not double-blind, leading to concerns or a high risk of bias for deviations from intended interventions.

For most outcomes, only two studies were assessed as low risk of bias. The risk of bias for readmission to hospital was generally considered to have some concerns, while the outcome of relapse/exacerbations of psychosis was judged to be at high risk of bias for nearly half of the studies. Outcomes related to tolerability and acceptability, such as leaving the study early due to side effects or any reason, were mostly judged to have some concerns. Functioning and quality of life outcomes, measured with various scales, were deemed to have some concerns or a low risk of bias overall.

Study name and year	*Quality of Life*	*Readmission*	*Study Dropouts (Adverse)*	*Functioning*	*Psychosis Relapse*	*Study Dropouts (Any Reason)*	*Side Effects*
Branchey 1981	NA	NA	NA	NA	High	NA	NA
Caffey 1964	NA	NA	NA	NA	High	NA	NA
Carpenter 1999	Some concerns	Some concerns	NA	Some concerns	Some concerns	Some concerns	NA
Cookson 1987	NA	NA	NA	NA	Some concerns	NA	Some concerns
Faraone 1989	NA	Some concerns	NA	NA	Some concerns	NA	NA
Fleischhacker 2014	NA	Low risk	Low risk	Some concerns	Low risk	Low risk	Low risk
Hirschowitz 1995	NA	NA	NA	NA	NA	NA	NA
Hogarty 1988	NA	NA	NA	NA	High risk	High risk	NA
Hogarty 1995	NA	NA	NA	NA	NA	NA	NA
Huhn 2020	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Johnson 1987	NA	NA	NA	NA	Low risk	NA	NA
Kane 1983	NA	Some concerns	NA	NA	Some concerns	Some concerns	NA
Kane 2010	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Some concerns
Kinion 2000	NA	NA	NA	NA	NA	NA	NA
Lonowski 1978	NA	NA	NA	NA	Some concerns	NA	NA
Newcomer 1992	NA	NA	NA	NA	NA	NA	NA
Ozawa 2019	NA	NA	Some concerns	Some concerns	High risk	Some concerns	NA
Remington 2011	NA	Some concerns	Some concerns	NA	High risk	NA	NA
Rouillon 2008	High risk	High risk	High risk	NA	High risk	Some concerns	High risk
Schooler 1997	NA	High risk	NA	NA	Some concerns	NA	NA
Takeuchi 2014	High risk	NA	Low risk	NA	High risk	Some concerns	NA
Volavka 2000	NA	NA	Some concerns	NA	NA	Some concerns	NA
Wang 2010	NA	NA	NA	NA	High risk	NA	NA
Wunderink 2007	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	NA
Zhou 2018	NA	Some concerns	Some concerns	NA	Some concerns	Some concerns	NA

Table A4: Overall Risk of Bias of Included Studies by Outcome

Effects of interventions

Primary outcomes

The review's exploration of primary outcomes revealed that while **quality of life** was a key area of interest, it was not reported in terms of clinically important changes by any of the studies included in the review.

For the outcome related to **service use**, specifically **hospital readmission** rates, the meta-analysis of eight studies indicated a trend suggesting that participants on a maintained dose of antipsychotics might have a lower likelihood of readmission compared to those whose doses were reduced. The risk ratio (RR) was 1.53, with a 95% confidence interval (CI) of 0.84 to 2.81, reflecting moderate heterogeneity ($I^2 = 59\%$) and very low certainty evidence. This trend did not reach statistical significance. Sensitivity analyses, which included the removal of studies with a high risk of bias and the application of a fixed-effect model, produced similar results, indicating the robustness of the initial findings.

Adverse effects, specifically the **rate at which participants discontinued the study due to adverse effects, were** also examined. The meta-analysis, which included data from ten studies, found that participants in the dose maintenance group were less likely to leave the study early due to adverse effects compared to those in the dose reduction group. The risk ratio was 2.20, with a 95% CI of 1.39 to 3.49, and there was no observed heterogeneity ($I^2 = 0\%$), suggesting moderate certainty evidence. Sensitivity analyses confirmed the stability of these results, with no significant changes after excluding studies based on various risk factors. The fixed-effect model corroborated these findings due to the absence of statistical heterogeneity.

Secondary outcomes

In the review's secondary outcomes, the **quality of life** was assessed across six studies, which showed no significant difference between maintaining and reducing antipsychotic doses (SMD −0.01, 95% CI −0.17 to 0.15, 6 RCTs, n = 719, I^2 = 0%, P = 0.63).

Functioning was similarly assessed with no significant difference found between the two groups (SMD 0.03, 95% CI −0.10 to 0.17, 6 RCTs, n = 966, I^2 = 0%, P = 0.62).

Global state outcomes included **relapse/exacerbations of psychosis**, with participants in the dose reduction group having a higher risk of relapse (RR 2.16, 95% CI 1.52 to 3.06, 20 RCTs, n = 2481, I^2 = 70%, P = 0.33). **Remission rates** showed no significant difference between groups (RR 0.82, 95% CI 0.61 to 1.09, 1 RCT, n = 397). **Clinically important changes in global state** also showed no significant difference at less than three or six months. CGI-S and CGI-I scales reported no significant differences (CGI-S: MD 0.05, 95% CI −0.18 to 0.28, 6 RCTs, n = 999, I^2 = 66%, P = 0.91; CGI-I: MD 0.19, 95% CI −0.47 to 0.85, 3 RCTs, n = 881, I^2 = 89%, P = 0.81). SCL-90 results favored dose reduction at all time points (less than three months: MD −0.38, 95% CI −0.61 to −0.15; less than six months: MD −0.52, 95% CI −0.80 to −0.24; less than one year: MD −0.59, 95% CI −0.91 to −0.27).

Leaving the study early for any reason was lower in the dose maintenance group (RR 1.38, 95% CI 1.05 to 1.81, 12 RCTs, n = 1551, I^2 = 48%, P = 0.83), and **leaving early due to inefficacy** was higher in the dose reduction group (RR 2.06, 95% CI 1.21 to 3.50, 10 RCTs, n = 1322, I^2 = 38%, P = 0.08).

Clinically important changes in general mental state were higher in the dose maintenance group (RR 0.84, 95% CI 0.75 to 0.94, 2 RCTs, n = 417, I^2 = 0%, P = 0.62). **Mental state** measured with PANSS and BPRS showed no significant difference (SMD 0.02, 95% CI −0.24 to 0.27, 12 RCTs, n = 1718, I^2 = 80%, P = 0.60).

Weight gain was lower in participants with dose reduction (RR 0.39, 95% CI 0.25 to 0.61, 3 RCT, n = 883, P = 0.93). **Changes in weight (kg)** showed no significant difference (MD −0.80, 95% CI −2.14 to 0.53, 6 RCTs, n = 1074, I^2 = 81%, P = 0.14).

Adverse effects evaluated with LUNSERS and UKU scales showed no significant difference (SMD −0.01, 95% CI −0.34 to 0.31, 2 RCTs, n = 147,

I^2 = 0%, P = 0.95). **Extrapyramidal symptoms** measured with multiple scales indicated a small difference favoring dose reduction (SMD −0.17, 95% CI −0.32 to −0.03, 9 RCTs, n = 1532, I^2 = 35%, P = 0.48).

Overall mortality showed no significant difference between dose reduction and maintenance (RR 2.69, 95% CI 0.48 to 15.05, 5 RCTs, n = 941, I^2 = 0%, P = 0.88). **Mortality due to natural causes** and suicide also showed no significant difference (natural causes: RR 1.51, 95% CI 0.16 to 14.02, 3 RCTs, n = 906, I^2 = 0%, P = 0.49; suicide: RR 6.07, 95% CI 0.25 to 147.95, n = 397).

Cognition showed a significant difference favoring dose reduction (SMD −0.74, 95% CI −1.08 to −0.39, 2 RCTs, n = 136, I^2 = 0%, P = 0.08).

The average baseline and endpoint doses of antipsychotics, converted to olanzapine equivalents, varied across studies, with no differences between groups at baseline.

Discussion

The review identified 25 studies eligible for inclusion, with 22 studies providing data for the meta-analyses, involving 2635 participants. The evidence ranged from very low to high certainty for various outcomes, with dose reduction associated with a higher number of participants experiencing psychotic relapse, leaving the study early due to adverse effects, and leaving the study for any reason. These effects were not offset by improvements in quality of life or functioning, as no difference was found between groups for these outcomes. However, caution is advised due to the varying levels of certainty and potential methodological heterogeneity across studies.

The general mental state, as a clinically important change, improved for the continuation arm, but this was not confirmed by scale-measured outcomes using PANSS, BPRS, or CGI. Similar results were found for positive, negative, depressive, or anxiety symptoms and aggressive behaviors.

Dose reduction was associated with a clinically important change in weight gain, indicating fewer participants experienced weight gain, but this was not consistent across other weight change measures. A small decrease in extrapyramidal symptoms measured with scales was observed with dose reduction, but the number of participants with movement disorders symptoms did not differ between groups.

Cardiological, endocrinological, hematological, and other adverse effects did not differ significantly between dose reduction and maintenance, with results primarily reported in three studies (126, 131, 133). Mortality rates for any reason, natural causes, or suicide also showed no significant difference between the intervention and control arms.

Cognitive functioning improved in the dose reduction group, based on two RCTs with few participants, warranting further investigation.

The review follows Cochrane standards and integrates up-to-date methods for estimating evidence certainty, aiding clinical decision-making. However, the generalizability of functioning and quality of life data is limited, and the interpretation of results is cautioned due to the primary aim of many included studies being relapse prevention rather than dose reduction.

Most evidence for prespecified outcomes was burdened by high statistical heterogeneity, potentially due to variability in the degree and speed of dose reduction, route of administration, participants, and range of drugs.

The GRADE approach assessed the certainty of evidence as very low for service use readmission to the hospital, moderate for quality of life, adverse effects, and leaving the study early, and high for functioning. The review process had potential biases, including an outdated search, focus on dose reduction studies, and exclusion of Chinese manuscripts.

The review's findings are in partial agreement with other studies, such as Tani 2020 (169), which also found lower relapse rates in the dose continuation arm.. Similar to Tani 2020, psychopathology and quality of life did not differ between dose maintenance and reduction groups in this review. Cognitive improvement with dose reduction was consistent with Tani 2020, while extrapyramidal scale scores were slightly lower in the dose reduction arm in this review. Weight gain findings were similar to Tani 2020, with fewer participants experiencing clinically important weight gain in the dose reduction arm.

Authors' Conclusion

The evidence from this review indicates that reducing the dose of antipsychotics is associated with a higher risk of relapse in individuals with

schizophrenia. While most adverse effects did not show significant improvement with dose reduction, there were notable exceptions, such as extrapyramidal symptoms and weight gain. However, the data on specific adverse effects were limited, preventing conclusive statements.

The studies included in the review were often dated and lacked robust design, with insufficient details on the dose reduction schemes. Among current schizophrenia treatment guidelines, the topic of dose reduction is thoroughly addressed only in the Japanese guidelines (17), reflecting both the recency of these guidelines and the active interest of Japanese researchers in this area (119, 128, 170-172). Other guidelines typically recommend a shared decision-making approach to dose reduction (19, 21).

For future research, there is a need for new studies on dose reduction, particularly with second-generation antipsychotics. Researchers should prioritize patient-reported outcomes, such as quality of life and functioning, to provide a more holistic view of treatment effects beyond relapse risk. Detailed rationales and strategies for dose reduction should be provided, with recent studies suggesting various effective approaches (173, 174). Additionally, research should address the reduction of off-label doses to standard doses, a clinically relevant issue that remains underexplored.

Antipsychotic polypharmacy reduction versus polypharmacy continuation for people with schizophrenia

The ensuing section provides a detailed summary of the publication cited below:

Bighelli, I., Rodolico, A., Siafis, S., Samara, M. T., Hansen, W. P., Salomone, S., Aguglia, E., Cutrufelli, P., Bauer, I., Baeckers, L., & Leucht, S. (2022). Antipsychotic polypharmacy reduction versus polypharmacy continuation for people with schizophrenia. *The Cochrane database of systematic reviews*, *8*(8), CD014383. https://doi.org/10.1002/14651858.CD014383.pub2

Background

Antipsychotic medications play a crucial role in managing acute schizophrenia and preventing relapses, but they are not without significant side effects, including movement disorders, weight gain, and metabolic issues that contribute to increased mortality rates (3, 50, 51). There is also debate over the potential for antipsychotics to cause dose-related brain volume loss (52). Despite these concerns, high doses and antipsychotic polypharmacy are common in clinical practice, often driven by factors such as suicide risk, aggressive behavior, limited hospital resources, and non-response to treatment (53, 54). A systematic review indicated that 20% of schizophrenia patients are on polypharmacy, (55), and 10% are prescribed doses exceeding approved levels (56). Clinicians face the challenge of determining if and how to safely reduce high doses and polypharmacy while maintaining the benefits of relapse prevention during the maintenance phase of treatment. This may even involve complete withdrawal of antipsychotics for a subset of patients who remain episode-free for an extended period (84). However, there is a delicate balance to maintain, as too low a dose or discontinuation can lead to a high risk of relapse with serious patient consequences (50). The current Review synthesizes data from RCTs that compare the reduction of antipsychotic polypharmacy to maintaining the same number of antipsychotics.

Description of the condition

See "Description of the condition" paragraph in the dose reduction review.

Description of the intervention

Antipsychotic medications are the cornerstone of schizophrenia treatment, often required long-term to mitigate the risk of relapse due to the disorder's chronic nature (51). Despite their therapeutic benefits, antipsychotics come with a range of adverse effects that complicate their use, including movement

disorders, weight gain, metabolic issues, sexual dysfunction (50), potential brain volume loss (52), and an increased risk of mortality (4).

A significant challenge in treating schizophrenia is the high rate of non-response to antipsychotic medications, with 40% to 50% of patients not achieving even a minimal response (54, 175). This often leads clinicians to employ polypharmacy, combining multiple antipsychotics in hopes of enhancing efficacy (55). However, measuring the exact rates of non-response can be difficult due to issues like poor medication adherence.

Antipsychotic polypharmacy, which occurs in about 20% of cases (55), may involve augmentation strategies that target different receptor sites or aim to minimize adverse effects (71).

This review focuses on the intervention of reducing the number of antipsychotics prescribed during the maintenance phase of schizophrenia treatment. Reducing antipsychotic polypharmacy involves withdrawing one or more antipsychotics from a patient's regimen. It's important to note that while the number of antipsychotics may decrease, the overall dose might not change if the doses of the remaining medications are increased. The challenge lies in balancing the reduction to avoid the risk of relapse that can occur if the overall antipsychotic dose becomes too low (51).

How the intervention might work

While certain combinations of antipsychotics may offer therapeutic benefits (176), On the other side, combinations of antipsychotic drugs can lead to drug-drug interactions resulting in unexpectedly high or low plasma levels, for example by the inhibition or induction of cytochrome P450 enzymes in the liver, which are responsible for the metabolism of most psychotropic drugs (71). Such interactions, for instance between haloperidol and olanzapine, require careful monitoring. However, plasma level monitoring can be costly and is not universally accessible (71). Additionally, polypharmacy may result in excessively high overall doses of antipsychotics. Research, particularly on first-generation antipsychotics, suggests that relatively low doses are sufficient to achieve the dopamine receptor blockade necessary for antipsychotic efficacy (177).

Theoretically, reducing polypharmacy by withdrawing one or more antipsychotics could alleviate issues related to drug-drug interactions, lower

the total antipsychotic burden, and decrease the adverse effect load for individuals with schizophrenia (178-180). This reduction may also improve medication adherence and decrease treatment costs. However, there are potential risks, such as the possibility that patients may require the drug combinations they are on, or that the overall dose may become too low after withdrawal, leading to relapse (51). This review aims to evaluate the evidence and provide insights into the potential advantages and drawbacks of reducing antipsychotic polypharmacy.

Why it is important to do this review

Antipsychotic medications are recognized for their effectiveness in both the acute treatment of schizophrenia and in preventing relapses(50, 51). However, they are associated with significant adverse effects, including movement disorders, weight gain, and metabolic issues, which may contribute to the notably higher mortality rates observed in this population (3). There is also a contentious debate regarding the potential for antipsychotics to cause dose-related brain volume loss, although distinguishing such changes from those caused by the illness itself or other factors is challenging(52, 81, 83).

In clinical practice, particularly when managing acutely ill patients, there is a tendency to use antipsychotic polypharmacy, often due to the urgency of addressing risks like suicide or aggressive behavior, pressures for shorter hospital stays, and high rates of non-response to treatment (53-55). Despite this, clinical guidelines generally advise against the use of multiple antipsychotics concurrently due to the risk of drug-drug interactions and the limited evidence supporting the efficacy of such an approach (181). The question of whether antipsychotic polypharmacy can be safely reduced during the maintenance phase of schizophrenia treatment remains unanswered (182). This review aims to systematically summarize data from all relevant randomized controlled trials (RCTs) to provide high-quality evidence on the effects of reducing antipsychotic polypharmacy compared to maintaining it in individuals with schizophrenia who are stabilized on antipsychotic treatment. The findings are particularly relevant for informing clinical guidelines and policy decisions, given the substantial societal costs associated with the disability resulting from schizophrenia (88).

Objectives

The review aims to evaluate the effects and safety of reducing antipsychotic polypharmacy versus maintaining individuals with schizophrenia on their current regimen of multiple antipsychotics. It also seeks to investigate the factors involved in the reduction of polypharmacy, such as the number of antipsychotics that are discontinued and whether the reduction is offset by an increase in the dosage of the remaining medications. This examination will provide insights into the potential benefits and risks associated with altering antipsychotic treatment strategies for people with schizophrenia.

Methods

The methods of this review align with dose reduction review except for the following paragraphs.

Types of interventions

1.Antipsychotic polypharmacy reduction

Reduction in antipsychotic medication, initially involving a minimum of two types, regardless of the specific drugs, quantity, or withdrawal rate. Applies to antipsychotics approved in at least one country.

2.Antipsychotic polypharmacy continuation

Continuation of the current number of antipsychotics.

Search methods for identification of studies

Cochrane Schizophrenia Group's Study-based Register of Trials

The Cochrane Schizophrenia Group's Study-Based Register of Trials was searched on February 10, 2021, using the term **Polypharmacy** in the intervention field of the study.

Subgroup analysis and investigation of heterogeneity

The study will examine the effects of reducing antipsychotic polypharmacy in several aspects. Firstly, the extent of reduction, involving the withdrawal of varying numbers of antipsychotics, will be analyzed. This aspect considers the balance between reducing adverse effects and quality of life improvement against the increased risk of major relapses and rehospitalization. Secondly, the approach to reduction will be categorized based on its speed, differentiating between abrupt and gradual methods. A rapid reduction may heighten the risk of significant relapses. Finally, the initial count of

antipsychotics prescribed to participants will also be considered, as results could vary based on whether they started with two or more medications.

Sensitivity analysis

In certain studies, decreasing the number of antipsychotic drugs is offset by increasing the dosage of the remaining ones. This approach could be beneficial over maintaining polypharmacy due to reduced drug-drug interactions. A sensitivity analysis is planned to exclude these trials.

Results

Summary of findings table

Outcome	*Polypharmacy Reduction*	*Polypharmacy continuation*	*Relative Effect (95% CI)*	*Total Participants*	*Certainty of Evidence*
Quality of Life	-	-	-	-	-
Hospital Readmission	108 per 1000	81 per 1000	RR 0.75 (0.25 to 2.24)	127 (1 RCT)	Very low
Study Dropouts (Adverse)	11 per 1000	49 per 1000	RR 4.37 (0.77 to 24.88)	176 (3 RCTs)	Very low
Functioning	-	-	MD 0.66 higher	12 (1 RCT)	Very low
Psychosis Relapse	-	-	-	-	-
Study Dropouts (Any Reason)	327 per 1000	144 per 1000	RR 0.44 (0.29 to 0.68)	319 (5 RCTs)	Low
Side Effects	0 per 1000	0 per 1000	RR 5.00 (0.28 to 88.53)	14 (1 RCT)	Very low

Table B1. Summary of findings table

Description of included studies

The review conducted a search through the Cochrane Schizophrenia Group register of trials and identified 25 studies for full-text screening. After the screening process, 18 studies were excluded, one study is awaiting classification, and five studies were included in the review and quantitative synthesis. These included studies encompassed a total of 319 participants and were reported across nine different reports (182-186). No ongoing studies were found.

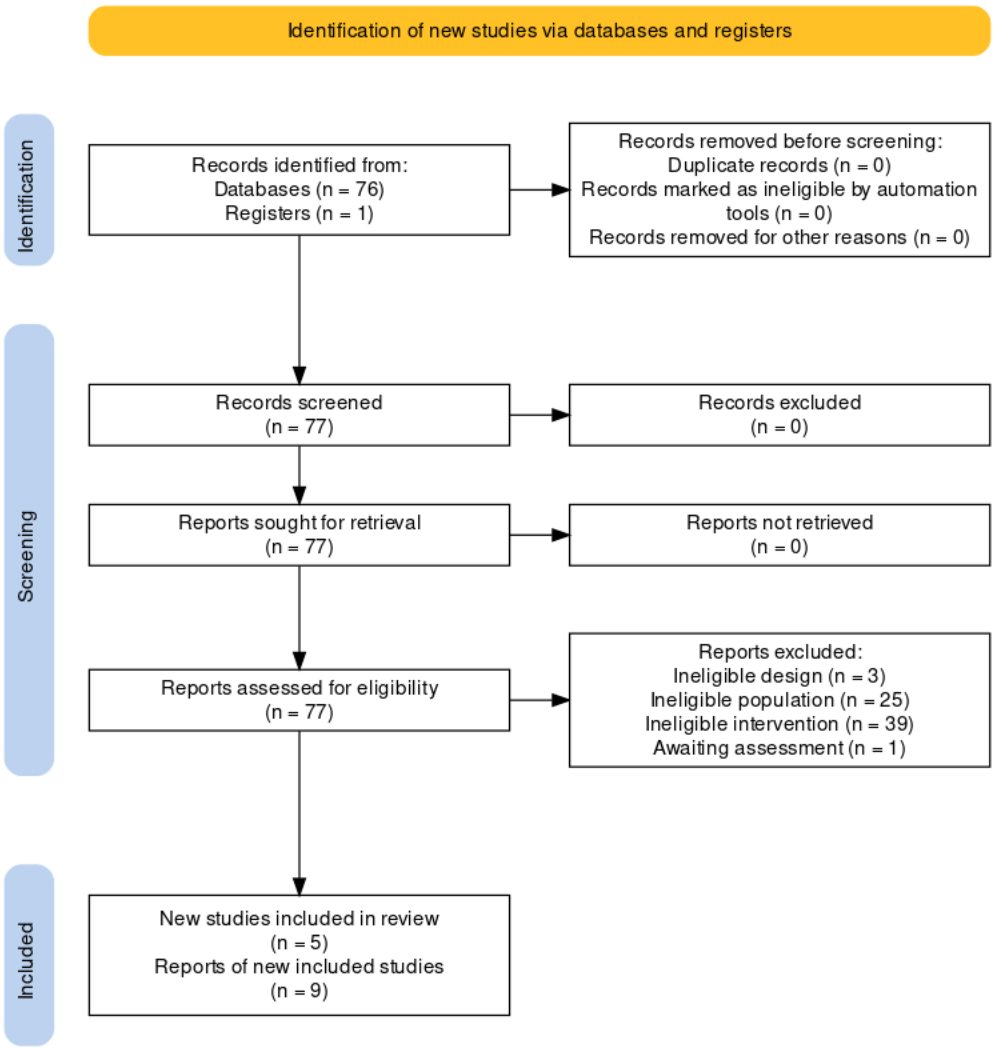

Figure B1. Prima flowchart

All five included studies were randomized controlled trials (RCTs), with one employing a cross-over design, from which only data from the first phase were used. The duration of the studies varied, with two lasting three months, two extending to six months, and the longest study running for one year.

The diagnostic criteria for schizophrenia varied across studies, with two using DSM-IV, two using DSM-IV-TR, and one study not specifying the diagnostic criteria. One study specifically targeted treatment-resistant individuals. The average age of participants across the studies was approximately 45.3 years.

The size of the studies ranged from 14 to 127 participants, with an average of 64 participants per study. The settings included a Department of Forensic Psychiatry for inpatients, outpatient settings, and one study that included both inpatients and outpatients.

Intervention-wise, all studies compared the continuation of treatment with two antipsychotics to a reduction to one antipsychotic. Most studies planned the reduction to occur over several weeks, although one study did not detail the speed of polypharmacy reduction.

Included studies are described in table B2.

Study name and year	*Country*	*Clinical state*	*Drug used*	*Polypharmacy reduction strategy (compensation)*	*Polipharmacy reduction degree*	*Duration*	*Number of participants*	*Average age of participant*
Borlido 2016	Canada	Not specified	Multiple	No information (Yes)	From 2 to 1	12	35	47.5 years
Constantine 2015	USA	Chronically ill	Multiple	Gradual (No)	From 2 to 1	52	104	45.5 years
Essock 2011	USA	Partial remission	Multiple	Gradual (Yes)	From 2to 1	26	127	47 years
Hori 2013	Japan	Chronically ill, partial remission	Multiple	Gradual (Yes)	From 2 to 1	24	39	36.4 years
Repo-Tiihonen 2012	Finland	Chronically ill, treatment-resistant	Olanzapine, Clozapine	Gradual (Unclear)	From 2 to 1	12	14	47.58 years

Table B2. Included studies

Outcomes

The studies included in the review employed a range of scales to measure various outcomes. For functioning, the Global Assessment of Functioning (GAF) (127) was used in one study (186). The global state of participants was assessed using the Clinical Global Impression (CGI) scale (138) in two studies (183, 186). Mental state was evaluated with the Brief Psychiatric Rating Scale (BPRS) (144) in one study (183) and the Positive and Negative Syndrome Scale (PANSS) (145) in two studies (182, 185).
Cognition was measured using the Brief Assessment of Cognition in Schizophrenia – Japanese version (BACS-J) (187) in one study (185).

Funding sources

All studies reported a public funding.

Excluded studies

The review process led to the exclusion of 19 studies following a full-text assessment. The reasons for exclusion varied, including issues such as non-randomized study design (188-190) populations without a schizophrenia diagnosis or with acute/agitated and unstable schizophrenia (191); acute/agitated, participants with unstable schizophrenia (192-197) and interventions that did not involve a reduction in antipsychotic polypharmacy (170, 172, 198-204).
One study is awaiting classification due to uncertainties regarding the stability of the participants' phase and the lack of usable data (205). Despite attempts to contact the authors, no response was received. No ongoing studies met the eligibility criteria for inclusion.

Risk of bias

The risk of bias for the included studies was assessed as having 'some concerns' or being 'high'. While studies described their allocation as randomized, many did not provide sufficient details on the sequence generation process. Baseline differences were generally not significant enough to indicate issues with randomization. However, three studies were

not double-blind, leading to some concerns or high risk of bias in the domain of "Deviations from intended interventions".

Specifically, the outcome of readmission to hospital was considered at high risk of bias, with data coming from a single open-label study that showed deviations from intended interventions between groups (182). Functioning, as measured by rating scales, was also deemed at high risk of bias, with the information coming from only one study that had issues with missing outcome data (186).

Study name and year	*Quality of Life*	*Readmission*	*Study Dropouts (Adverse)*	*Functioning*	*Psychosis Relapse*	*Study Dropouts (Any Reason)*	*Side Effects*
Borlido 2016	NA	NA	Some concerns	NA	NA	Some concerns	NA
Constantine 2015	NA	NA	NA	NA	NA	High risk	NA
Essock 2011	NA	High risk	High risk	NA	NA	High risk	NA
Hori 2013	NA	NA	NA	NA	NA	Some concerns	NA
Repo-Tiihonen 2012	NA	NA	Some concerns	High	NA	Some concerns	Some concerns

Table B4: Overall Risk of Bias of Included Studies by Outcome

Effects of interventions

Primary outcomes

None of the included studies reported on **clinically important changes in quality of life**, suggesting an area ripe for future research efforts.

Regarding service use, reported here by **hospital readmission rates**, the review's scrutiny of one study offered hinted at no significant difference in readmission rates between ongoing polypharmacy and reduction to a single antipsychotic. This was quantified by a risk ratio (RR) of 0.75, with a 95% confidence interval (CI) ranging from 0.25 to 2.24, coupled with very low certainty and moderate heterogeneity.

Adverse effects, particularly the propensity of participants to discontinue the study early due to such effects, were also a focal point. The combined analysis of three randomized controlled trials suggested a trend favoring reduced polypharmacy. The participants in the reduced polypharmacy group were less likely to leave the study early due to adverse effects, denoted by a risk ratio of 4.37 and a 95% confidence interval from 0.77 to 24.88. This outcome exhibited no heterogeneity ($I^2 = 0\%$) and was marked by very low certainty evidence. Sensitivity analyses, including the exclusion of high-risk bias studies and the application of a fixed-effect model, were in line with the original findings.

Secondary outcomes

No studies reported on the **mean endpoint or change score on the quality-of-life scale, days in hospital, or clinically important change in functioning**. One study did report on the **mean endpoint on the functioning** scale using the GAF scale, finding no evidence of a difference between continuation of polypharmacy and reduction to one antipsychotic (MD 0.66, 95% CI −5.89 to 7.21; 1 RCT, n = 12; very low-certainty evidence). The same

study also reported on the mean change score on the functioning scale with similar findings (MD −0.77, 95% CI −2.75 to 1.21; 1 RCT, n = 12).

Regarding **global state**, one study reported on clinically important change in global state (improvement) with no evidence of a difference between the two groups (RR 1.11, 95% CI 0.58 to 2.14; 1 RCT, n = 28). Two studies reported on the mean endpoint score using the CGI-I scale, also showing no evidence of a difference (MD 0.32, 95% CI −0.32 to 0.96; 2 RCTs, n = 40). One study could not estimate an effect size for the mean change score using the CGI-I scale because the mean change in one group was zero (1 RCT, n = 12).

For the outcome of **leaving the study early**, participants who continued polypharmacy were less likely to leave the study early compared to those who reduced polypharmacy (RR 0.44, 95% CI 0.29 to 0.68; 5 RCTs, n = 319; low-certainty evidence). This was consistent at up to six months and one year, with no subgroup differences detected (P = 0.80). Participants were also less likely to leave early due to inefficacy in the continuation group (RR 0.21, 95% CI 0.07 to 0.65; 3 RCTs, n = 201).

No studies reported on **relapse/exacerbations of psychosis, clinically important changes in general mental state, positive symptoms, negative symptoms, depressive symptoms, behavior (including aggression), satisfaction with care, or clinically important changes in cognition**. One study reported on mean endpoint or change score on the PANSS Total scale, BPRS scores, and PANSS Positive scale, with no evidence of a difference between continuation and reduction of polypharmacy.

Adverse effects were reported in one study, with no evidence of a difference in **at least one adverse effect** (RR 5.00, 95% CI 0.28 to 88.53; 1 RCT, n = 14; very low-certainty evidence). No studies reported **clinically important changes in weight**, but one study reported on **mean BMI change**, showing a trend towards lower BMI in the reduction group (MD 0.78, 95% CI −0.03 to 1.59; 1 RCT, n = 127). **Weight measured in kilograms** also showed no evidence of a difference between groups at up to three and six months.

Specific adverse effects such as **tardive dyskinesia and extrapyramidal symptoms** showed no evidence of a difference between groups. **Mortality** outcomes, including overall mortality, mortality due to natural causes, and suicide, could not be estimated due to zero events in both groups (1 RCT, n = 14).

Medication doses at endpoint, converted to olanzapine equivalents, showed no evidence of a difference between continuation and reduction of polypharmacy (MD 2.71, 95% CI −1.60 to 7.02; 1 RCT, n = 35). **Cognition**, reported in one study, also showed no evidence of a difference (MD 0.11, 95% CI −0.22 to 0.44; 1 RCT, n = 35).

Due to the small number of studies included in the analyses, a funnel plot was not created to assess publication bias.

Discussion

This review identified five studies with a total of 319 participants eligible for inclusion. The findings, based on low to very low-certainty evidence, suggest that reducing the number of antipsychotics compared to continuing treatment with multiple antipsychotics is associated with a higher number of participants leaving the study early for any reason and due to inefficacy. The risk of bias for the outcome of leaving the study early was rated as having 'some concerns' to 'high'.

The reduction in the number of antipsychotics was linked to a decrease in negative symptoms, as reported by one RCT with 35 participants. There was also a trend favoring polypharmacy reduction in the number of participants leaving the study early due to adverse effects, although the confidence intervals did not exclude the possibility of no difference.

Polypharmacy reduction might be associated with a decrease in BMI and weight gain, but the evidence from only one study was not conclusive. Similarly, the reduction might be associated with a decrease in antipsychotic dose, but again, the evidence from a single study was not definitive.

No difference was observed between continuation and reduction of polypharmacy regarding readmission to hospital and the number of

participants leaving the study early due to adverse effects. No data were available for the primary outcome of quality of life.

In summary, more participants dropped out in general with polypharmacy reduction, mainly due to inefficacy, while fewer may have dropped out due to adverse effects compared to continuing treatment with two antipsychotics. Reducing antipsychotic polypharmacy may reduce efficacy on one hand but also lessen the burden of adverse effects on the other.

The review's findings were limited by the small number of studies and participants, with many outcomes based on a single study. The analyses may have been underpowered, particularly for outcomes like leaving the study early due to adverse effects, BMI, and weight gain, where there was a trend suggesting a benefit with antipsychotic polypharmacy reduction, but the confidence intervals did not rule out the possibility of no difference.

All identified studies examined the reduction from two antipsychotics to one, so the findings cannot be generalized to situations where individuals are receiving three or more drugs. The certainty of the evidence was predominantly very low, indicating that further research could significantly impact the confidence in the effect estimates.

Using GRADE, the certainty of the evidence was assessed as very low for most outcomes, except for leaving the study early due to any reason, which was rated as low certainty. The evidence for service use readmission to hospital was rated as very low due to high risk of bias and imprecision. The evidence for leaving the study early due to adverse effects was also rated as very low, with downgrades for risk of bias and imprecision. Functioning was rated as very low certainty due to high risk of bias and a very low number of participants.

The review was limited by the overall risk of bias in the outcomes reported in the included studies. Preplanned subgroup analyses could not be performed, and only some sensitivity analyses were conducted, which were underpowered. It was not possible to determine if the reduction in the number of antipsychotics was compensated by increasing the doses of the remaining drugs, as only one study reported mean antipsychotic dose at endpoint.

The review's findings are consistent with another review (206), which also found no difference between polypharmacy reduction and continuation for

readmission to hospital and a trend favoring polypharmacy reduction in the number of participants leaving the study early due to adverse effects. However, our review showed a clear benefit for polypharmacy continuation on the outcome of leaving the study early due to inefficacy, while the other review only suggested a trend. For mental state, the other review found no difference for negative symptoms, whereas our review found a benefit for polypharmacy reduction based on one study. It did not report results on other outcomes.

Authors' Conclusion

The findings from this review are based on low to very low-certainty evidence and are underpowered, making it difficult to draw firm conclusions.

In clinical settings, some patients may prefer to continue with a combination of antipsychotics that has proven effective for their individual needs. Maintaining a trusting relationship with the treating clinician is crucial in determining the most appropriate and personalized treatment approach.

For future research, it is important to explore the effects of reducing treatment from more than two antipsychotic agents, in addition to the reduction from two to one. An individual participant data (IPD) meta-analysis could provide more insight into various factors that may influence the outcomes of antipsychotic polypharmacy reduction, such as the degree and speed of reduction, the initial number of antipsychotics, the specific agents withdrawn, the severity of illness, and other patient characteristics.

A companion review is currently examining the impact of dose reduction on multiple outcomes (207). Additionally, further research is needed to understand the most effective methods for implementing polypharmacy reduction, as this aspect remains uncertain (208, 209).

How should patient decision aids for schizophrenia treatment be designed?- A scoping review (Review)

The ensuing section provides a detailed summary of the publication cited below:

Müller, K., Schuster, F., Rodolico, A., Siafis, S., Leucht, S., & Hamann, J. (2023). How should patient decision aids for schizophrenia treatment be designed? - A scoping review. *Schizophrenia research*, *255*, 261–273. https://doi.org/10.1016/j.schres.2023.03.025

Introduction

The concept of shared decision-making (SDM) has gained traction in recent years, promoting patient involvement in medical decisions to enhance understanding of their condition, treatment options, and to foster treatment adherence (38, 210, 211). Despite its benefits, SDM has not been widely adopted in the routine treatment of schizophrenia. Many patients with schizophrenia report feeling inadequately involved in decision-making (212, 213) and clinicians often cite time constraints and heavy workloads as barriers to implementing SDM (213, 214). Clinicians may also doubt their patients' capacity to make decisions due to symptoms such as lack of disease insight and cognitive impairments associated with schizophrenia (215).

Patient decision aids (pDAs) have emerged as a promising tool to facilitate SDM by providing patients with clear information about the advantages and disadvantages of various treatment options, helping them articulate their preferences and engage actively in decision-making. These aids are ideally evidence-based, aligning with the principles of evidence-based medicine (EBM) to support "evidence-based patient choice"(216-218).

In somatic medicine, decision aids have been shown to improve patient knowledge and involvement in decision-making, serving as a practical means to operationalize SDM in clinical practice (219-221). The International Patient Decision Aid Standards (IPDAS) collaboration has set quality standards for decision aids, covering aspects such as information presentation, decision-making processes, underlying evidence, development process, and quality criteria(47).

The mental health field has also seen a surge in the development of decision-making support tools. A recent review by Alarcon-Ruiz et al. (222), examined decision aids in the context of depression treatment. Interest in decision aids for schizophrenia treatment has grown, likely because choosing between antipsychotics is a "preference sensitive decision" (223), , where the best

choice depends on individual risk-benefit assessments (224, 225). This is particularly relevant given the slight differences in efficacy but significant variation in side effect profiles among antipsychotics (42, 226), and the wide array of available medications complicating the selection process. While other treatments like psychotherapeutic and psychosocial interventions are effective and recommended (21), this review focuses on drug treatment due to the specific considerations mentioned.

Despite the strong rationale for using SDM and the development of several decision aids, there is still a lack of evidence on the key features and quality indicators essential for pDAs in schizophrenia treatment. Most existing tools lack data from randomized controlled trials. This review aims to survey the current tools and discuss recommendations for the future development and evaluation of pDAs in schizophrenia treatment.

Methods

The review team carried out a scoping review following the PRISMA-SRc guidelines (227), to map out the current landscape of decision aid tools designed for presenting medical evidence about antipsychotics to patients with schizophrenia. Scoping reviews serve as an appropriate method for synthesizing evidence on emerging topics where the research and concepts are still developing, such as decision aid tools (228). Unlike systematic reviews, which aim to critically evaluate and summarize literature to address specific clinical questions or guide practice, scoping reviews are more exploratory and aim to identify key concepts, research conduct, and gaps in evidence within a given field (228).

Eligibility criteria

Eligibility criteria for the review included studies addressing decision aids that presented medical evidence of antipsychotic drugs to patients with schizophrenia, regardless of their design. Decision aids without a component of presenting medical evidence on treatments were excluded.

Study search and selection

The search was conducted in PubMed from 1.7.2010 to 10.05.2021 using specific keywords related to shared decision-making, schizophrenia, and antipsychotics. The search was limited to the most recent ten years and had

no language or country restrictions. Two independent reviewers screened the records and selected eligible studies.

Focus of the investigation

The focus of the investigation was not on assessing the quality of decision aids, which could be done using the International Patient Decision Aid Standards instrument (IPDASi) developed by Elwyn et al.(47), but rather on how a decision aid for schizophrenia treatment with antipsychotics should be optimally designed. The review team screened the IPDAS criteria and derived seven core aspects for investigating the included decision aids: type, values, decision guidance, output, target group, evidence of data, and decision aid evaluation.

The review explored whether decision aids were offered in analog or digital form, how they helped patients clarify their values in relation to treatment decisions, and whether they included a structured approach to decision-making. It also examined how treatment options were presented, whether the decision aids were intended for use by patients alone or in conjunction with psychiatrists, and if they addressed any third parties such as caregivers.

A critical aspect was the evidence source used for the decision aids and the level of evidence of these sources, with systematic reviews, network meta-analyses, and randomized controlled trials considered the highest level of evidence. Lastly, the review assessed whether the decision aids had been systematically evaluated and the results of such evaluations.

Data extraction

The review process involved two independent reviewers who meticulously extracted relevant information from the included articles. They compiled details such as the author, year of publication, title, and key characteristics of the decision aids—type, values, decision guidance, output, target group, evidence source, and evaluation of the decision aid—into straightforward tables for easy reference. In instances where these authors encountered disagreements during the study selection or data charting phases, they engaged in discussions with senior authors to reach a consensus. If disagreements persisted and a consensus could not be reached through discussion, the reviewers reached out directly to the study authors to obtain additional information and clarify any uncertainties.

Results

From the 857 records identified in the initial search, eleven studies addressing six unique decision aid tools met the eligibility criteria for the review. A detailed description is presented in Table C1.

Tool Name	*WEGWEIS (213, 229)*	*COMPASS (230-232)*	*TREAT (233)*	*The Personal Antipsychotic Choice Index (234)*	*Encounter Decision Aid (235)*	*In Control of Effects (236)*
Type	Digital	Digital	Digital	Digital	Paper-based	Digital
Target Population	FEP + LTP	FEP	PD	Developed on FEP	Stabilized FEP + LTP	N/A
Clarified Values	Yes	No	No	No	Yes	Yes
Guidance Provided	Yes	Yes	No	Yes	No	Yes
Decision Output	Opt	Opt	Opt	Rnk	Opt	Rnk
User Groups	Pt	Clin & Pt	Clin (+ Pt)	Clin & Pt	Clin & Pt & CG	Clin & Pt/CG
Data Source	Ext	Ext	Ext	Ext	Ext	Int
Evidence Base	EO + SUE	LR	G + EO	Ch&SR&MA + EO + PC	SR&MA + G + RC	NMA
Development Process	Routine Monitoring	Literature Review	End-user input	Expert defined outcomes + Literature review	Expert summarized scientific literature	End-users > summarized in the App
Presentation	One homepage and three webpages (On presentation of results)	Webpage (multiple pages containing treatment guidance combining patient preferences + self-report with prescriber guidance and a summarizing webpage in the end)	Webpage (multiple domains + Experts predefined cutoff for ROM)	Six webpages (Pt info, and outcomes presentation)	Printed treatment options grid with benefits, risks and implications of different decisions	Offline DDA with three sections: instructions, side effect selection and results
User Feedback	Satisfaction incl. 6 items level towards the DA (+)	Not reported	Usefulness (+) Easy to use (+) Wish to use it in the future (+) Autonomy reduction (−) Behavorial control (−)	Not reported	Value (+) Acceptability (+/-)	Usefulness (+) Improves confidence (+/-) Starting point for discussion of preferences (+) Layout (+/-)
Clinical Testing	RCT	RCT	Feasibility study	Focus group	Focus group	Focus group

CG: Caregivers; Ch: Cochrane; Cln: Clinician; DDA: Digital Decision Aid; EO: Expert Opinion; Ext: External; G: Guidelines; Int Internal; LR: Literature Review; MA: Meta-analysis; NMA: Network Meta-Anlysis; Opt: Options to be discussed; PC: Pre-clinical; PD: Generically Psychotic Disorder; Pt: Patients; RCT: Randomised Controlled Trials; Rnk: ranking of antipsychotics; ROM: Routine Outcome Monitoring; SR: Systematic Review; SUE: Service User Experiences

Table C1: Details of Included Studies

Different types of decision aids

The studies investigated two main types of decision aids: paper-based and digital. Only one study used a paper-based "option grid" (235), while the rest examined digital tools, some of which could independently access clinical data (213, 229, 233).

Values

Three out of six decision aids supported patients in clarifying values related to choosing between antipsychotics. This support ranged from simple one-page grids to more complex web-based tools that provided information on treatment indications, duration, and content, as well as experiences from patients and physicians (213, 229).

Decision guidance

Decision guidance varied, with some aids offering a structured step-by-step approach, while others facilitated discussions between patients and providers without a fixed sequence (234-236).

Output of the decision aid

Outputs of decision aids included specific drug recommendations or more general treatment options. Some tools used algorithms to rank antipsychotics based on individual patient data (234, 236), while others provided treatment recommendations linked to clinical guidelines or encouraged discussions about treatment options (232, 233, 235).

Target group

All decision aids were designed for both patients and clinicians, with some emphasizing patient-prescriber communication and others encouraging individual use by patients or discussions with caregivers (232, 234, 235).

Evidence of data according to publication

The evidence sources for decision aids varied, with one aid relying on the highest level of evidence from a network meta-analysis (236), while others combined high-level evidence with lower-level sources to refine their tools (234).

Decision aid evaluation

Two decision aids were evaluated in randomized controlled trials, one focusing on patient involvement in decision-making and the other on the

impact of the NAVIGATE program on various outcomes (229, 230, 232). The NAVIGATE program, which included the COMPASS decision aid, showed positive effects on treatment duration, quality of life, psychopathology, and side effects (232). When comparing the two studies, it is noticeable that the implementation of the intervention in the NAVIGATE programme was clearly more strongly supported and the use of the decision aid in the hospital took place together with the physician. van der Krieke et al. (229), on the other hand, left it up to the patients to use the intervention together or alone, as well as at home or on site, which they also critically note in their limitations.

Other studies evaluated their decision aids for usability, acceptability, feasibility, and correctness, with suggestions for revisions to improve their effectiveness (233, 235, 236).

Discussion

The review on decision aids for schizophrenia treatment highlighted six distinct tools designed to present evidence on the efficacy and tolerability of antipsychotics to patients. The majority of these aids were digital, with half offering support for patients to clarify their values and providing structured decision-making steps. The presentation of treatment options varied, with two aids giving specific medication recommendations and the others presenting various options.

All the decision aids targeted both patients and clinicians, with one also addressing carers. While two aids were specifically for chronically ill patients, others were aimed at those with a first episode of psychosis or did not specify disease duration. The decision aids were based on diverse data sources, with only one exclusively using the highest level of evidence.

Evaluations of the decision aids varied, focusing on different clinical endpoints. There were notable differences in the design and development of the aids. Only one decision aid, developed by Zisman-Ilani et al., was explicitly designed according to the International Patient Decision Aid Standards (IPDAS) collaboration, using a paper-based option grid to answer common questions about antipsychotic medication (235). Other tools were developed with end-user involvement, providing suggestions and feedback, but not necessarily adhering to IPDAS criteria.

The inclusion of carers in the decision-making process was another key feature, although the literature is still debating the best ways to involve family caregivers in shared decision-making for patients with schizophrenia (237, 238). The review suggests that future decision aid designs should pay special attention to three main areas: the evidence base of the decision aid, the algorithm for translating evidence, and the presentation of evidence to users.

Evidence base of decision aids

The developers of decision aids for schizophrenia treatment generally aimed to incorporate data with a high level of evidence, aligning with recommendations for evidence-based patient decision aid tools (216). For instance, one decision aid was grounded in a comprehensive network meta-analysis of randomized controlled trials (RCTs) on antipsychotics (175). However, other decision support tools combined various levels of evidence due to the lack of high-quality data for certain specific questions. The "Personal Antipsychotic Choice Index," for example, prioritized effect sizes from RCTs and meta-analyses to rank medications but also included data from other sources when RCT evidence was unavailable (234). While the preference for high-level evidence from RCTs and meta-analyses is well-established for presenting information on antipsychotics, most reviewed decision aids also incorporated lower levels of evidence to address a broader range of questions. This approach is considered understandable and acceptable given the goal of patient-oriented decision aids to support individual decision-making among numerous medication options. The review recommends that the quality of the evidence base for decision aids should be graded (239) , with a preference for higher levels of evidence. The process of constructing the evidence base should be transparent, and future updates should be planned from the outset to ensure decision aids remain current. For example, an earlier network meta-analysis on the comparative efficacy and tolerability of antipsychotics (50) was updated to include newer trials and additional drugs and side-effects (42). Decision aids like "In Control of Effects," which used evidence from an updated version of the previous network meta-analysis (175), could be readily updated with the latest information. However, updates may be more challenging for decision aids

that used a more heterogeneous evidence base, such as the "Personal Antipsychotic choice index.

Bringing evidence together with patient preference

Developing a patient-centered decision aid for schizophrenia treatment presents challenges beyond having a robust evidence base. Medical evidence typically pertains to the average patient, derived from aggregate data, except in the rare cases where individual-participant-data meta-analyses are conducted. Evidence-based medicine emphasizes the need to tailor evidence from the average patient to the individual for a personalized treatment approach (240). However, applying "average" evidence to an individual is complex, as it must consider specific patient characteristics, such as varying treatment effects based on age, gender, or disease severity, as well as contraindications due to comorbidities or interactions with other medications. Additionally, clinician and patient preferences and values, such as the willingness to tolerate certain side effects or preferences for medication formulations, must be accounted for.

Decision aids are designed to bridge the gap between "average" evidence and individual patient characteristics and preferences. Algorithms are often employed for this purpose, functioning like a navigation system to provide medical guidance. However, current methods are not optimal and rely on assumptions that introduce imprecision and lack rigorous scientific support. For instance, the algorithm in the "Personal Antipsychotic Choice Index" (234) attempts to provide an individualized ranking of antipsychotics by combining medical evidence with patient preferences and values. This process involves expert consensus rankings, patient preferences collected via a Likert scale, and a predetermined weighting between efficacy and side effects. Despite the innovative approach, the required assumptions may limit the algorithm's flexibility and validity.

Future developments in evidence synthesis methods could enable more nuanced treatment recommendations at the individual level. New meta-analytic methods are being developed to incorporate patient characteristics, such as adjusting average treatment effects from network meta-analysis using individual-participant data (241), or patient preferences, like adjusting treatment rankings based on thresholds of clinically important effects (242).

An international team of experts is working to facilitate personalized antidepressant treatment for major depressive disorder by producing stratified treatment recommendations that integrate high-level evidence with patient and clinician preferences through a decision aid tool (243). However, even the most advanced algorithms must rely on assumptions that could challenge their application in shared decision-making. Such tools risk reducing decision-making to a computerized paternalistic process where the tool dictates the best treatment. Decision aids should therefore employ methods that provide a personalized view of the evidence without making the shared decision-making process overly rigid or assumption dependent.

Output of decision aids

The results section of the review reveals that most decision aids for antipsychotic treatment present their findings either as potential treatment options for discussion or as a hierarchical list of antipsychotic medications. For instance, the "In Control of Effects" decision aid combines patient input with the latest evidence to recommend the top three medications and the three antipsychotics to avoid (236). This straightforward presentation was well-received by patients, carers, and physicians for its anticipated ease of use. However, the complexity of choosing antipsychotic treatment was also highlighted, with a desire expressed for the inclusion of factors such as age or comorbidities in the decision-making process. While the simplicity of the output is advantageous, especially for acutely ill patients, it may overlook important factors that influence medication choice, such as previous medication complications. There is a concern that patients may not be sufficiently encouraged to consider their own values and needs, potentially leading to a hasty focus on a particular medication that may not be as suitable as it initially appears. In contrast, the more complex "TREAT" decision support tool (233) focuses on implementing patient-related data, including computerized questionnaires on antipsychotic tolerance, somatic comorbidities, and more, culminating in an interactive report summarizing evaluated symptoms, treatment effects, and unmet needs. However, this tool is primarily directed at physicians, who then communicate the results to the patient. While this approach may improve care by aligning treatment with guidelines, it remains to be seen whether it truly activates patients in a shared

decision-making process. The challenge with the output of decision aids for antipsychotics lies in activating the patient by presenting available treatment options, which is crucial for shared decision-making, while also catering to the specific needs of patients who may have cognitive deficits or lack illness insight. A potential solution is a scalable digital decision aid that can be adjusted based on the severity of cognitive impairment and disease stage. Additionally, complex outputs or multiple treatment options should be communicated in the presence of a physician or caregiver to ensure proper understanding and consideration. Implementation challenges also exist for decision aids. The typical hospital ward environment, often marked by time constraints and limited staff, makes it difficult for patients to process decision aids independently at home. As van der Krieke et al. (229) noted in their randomized controlled trial, this can lead to lower participation rates. It is worth considering whether the greater staff support in the COMPASS decision aid trial contributed to more valid results and better patient outcomes. The design requirements for a decision aid can vary significantly depending on the setting and level of support in which it is used.

Strengths and limitations

This article represents the first comprehensive overview of decision aids and their design in the context of treating patients with schizophrenia, covering developments over the past decade. The review aims to showcase the latest advancements in antipsychotic decision support tools and encourage further research to overcome the challenges identified. The decision not to quantify the International Patient Decision Aid Standards instrument (IPDASi) criteria was intentional, as the goal was to provide a broad perspective on the research landscape rather than assess the implementation of these criteria.

A limitation of this review is that only two decision aids have been evaluated in randomized controlled trials (RCTs), which restricts the ability to correlate specific features of decision aids with the outcomes of their clinical use. Additionally, the inherent nature of the review means that a quality assessment of the included studies is not feasible due to the diversity of study designs and the varying definitions of decision support tools. Moreover, the search was confined to the PubMed database, and future research could

benefit from expanding the search to include other established databases such as the Cochrane Library.

Conclusion

Decision aids are gaining traction in the treatment of schizophrenia, but applying standard quality criteria for patient-based decision aids to this patient group presents unique challenges due to the complexity of factors influencing decisions about antipsychotic treatment. Specific pitfalls arise concerning the evidence base, the algorithms used, and the presentation of results.

When developing decision aids for antipsychotics, it is recommended to rely on data with a high level of evidence and to incorporate mechanisms for updating the evidence base as new information becomes available. These aids should also prioritize the individualization of treatment recommendations by taking into account patient preferences, previous experiences, and the clinical judgment of the treating physician.

The algorithms employed to translate medical evidence to the individual patient should offer a flexible framework without relying on overly complex assumptions or leading to computerized paternalistic decisions. The presentation of results should be mindful of the potential cognitive deficits often experienced by patients with schizophrenia. The information provided should be as detailed as necessary yet as clear and understandable as possible to facilitate comprehension.

To honor the complexity of the decision-making process, decision aid tools for antipsychotics should be utilized by both the physician and the patient, ideally within the context of a collaborative discussion. This approach ensures that the decision-making process remains a shared endeavor, with both parties actively engaged in evaluating and selecting the most appropriate treatment option.

Evidence acquisition

Validation of the Glasgow Antipsychotic Side-Effect Scale (GASS) in an Italian Sample of Patients with Stable Schizophrenia and Bipolar Spectrum Disorders

The ensuing section provides a detailed summary of the publication cited below:

Rodolico, A., Concerto, C., Ciancio, A., Siafis, S., Fusar-Poli, L., Romano, C. B., Scavo, E. V., Petralia, A., Salomone, S., Signorelli, M. S., Leucht, S., & Aguglia, E. (2022). Validation of the Glasgow Antipsychotic Side-Effect Scale (GASS) in an Italian Sample of Patients with Stable Schizophrenia and Bipolar Spectrum Disorders. *Brain sciences*, *12*(7), 891. https://doi.org/10.3390/brainsci12070891

Introduction

Antipsychotic (AP) drugs are a cornerstone in the treatment of psychiatric conditions such as schizophrenia and bipolar disorder, playing a crucial role in managing symptoms, improving outcomes, and reducing relapses (41, 244-246). However, both first- and second-generation antipsychotics are associated with a range of side effects (SE) like weight gain, sedation, sexual dysfunction, cardiovascular issues, and extrapyramidal symptoms (42), which can significantly affect patients' quality of life and psychosocial functioning (247). Clinical guidelines recommend regular monitoring of SE to balance treatment efficacy with tolerability (19). Over the years, various scales have been developed to assess SE induced by AP treatment, some focusing on specific SE like extrapyramidal and sexual SE (248, 249), while others cover multiple SE categories (138, 157, 248). Some of them evaluate specific SE such as extrapyramidal and sexual SE (248, 249), while others are more extensive and consider various SE categories (156, 157). These scales are either hetero-administered or self-administered(156, 157, 248, 250), with the Udvalg for Kliniske Undersøgelser (UKU) SE rating scale for clinicians being the most widely used in research (156, 251). However, the UKU's time-consuming nature makes it challenging to use in everyday clinical practice, leading to recommendations for brief, self-report, multi-domain questionnaires for SE screening (251). The Glasgow Antipsychotic Rating Scale (GASS) has been endorsed by professionals and users as the standard patient-reported outcome measure for collecting data on AP-SE (30). The selection process for the GASS involved patient focus groups identifying key outcomes, stakeholders selecting "essential" outcomes, and assessment using the COSMIN checklist for psychometric properties (252). The GASS,

validated against the Liverpool University Neuroleptic Side-effect Rating Scale (LUNSERS) (157), is a concise self-assessment tool comprising 22 straightforward questions that patients can complete in about 5 minutes (34). Its advantages, including good discriminatory power, construct validity, and test-retest reliability, have been confirmed in direct validation against the UKU (35).

This work aimed to translate the GASS into Italian following standard practices and to evaluate its structural validity, internal consistency, concurrent criterion validity against the UKU scale, and clinical feasibility.

Methods

Participants

The participants for the study were recruited from the Psychiatry Unit of the University of Catania in Catania, Italy, and included both inpatients and outpatients. The inclusion criteria were comprehensive: participants had to be adults aged 18 years or older, diagnosed with a schizophrenia spectrum disorder or bipolar spectrum disorder according to DSM-5 criteria, and on antipsychotic (AP) treatment for at least six months. It was not necessary for participants to have been on the same AP consistently. Additionally, participants were required to be free of positive symptoms, as indicated by a score of 3 or less on specific items of the Positive and Negative Syndrome Scale (PANSS) inspired by Andreasen's remission criteria for positive symptoms. They also needed to be free of depressive or manic symptoms, as defined by scores on the Montgomery–Asberg Depression Rating Scale (MADRS) and the Young Mania Rating Scale (YMRS), have good insight (PANSS g12-lack of judgment & insight ≤ 3), and sufficient understanding of the questionnaires. Bipolar patients were required to be free of delusions and hallucinations, and all participants had to be capable of reading and understanding the informed consent documentation. Exclusion criteria were also established to ensure the appropriateness of the sample. Patients were excluded if they were undergoing compulsory treatment, had concomitant organic diseases, reported current use of psychoactive substances, had other neurological conditions such as epilepsy, movement disorders, intellectual disability, dementia, etc., or any condition that would prevent the completion of the assessment. Demographic and clinical data collected from participants

included age, sex, education, marital status, employment status, smoking status, concomitant pathologies, and illness-related data such as illness duration, hospitalizations, and the setting of actual recruitment. Drug-related data were also collected, including the antipsychotic used, olanzapine oral-equivalents, administration route, and concomitant psychotropic medications.

Instruments

The Glasgow Antipsychotic Side-effect Scale (GASS) is a self-administered questionnaire initially developed in English (34) and has been translated into various languages (35, 253, 254). It consists of 22 items that assess a range of side effects (SE) induced by antipsychotic (AP) medications, including weight gain, sedation, and effects on central nervous system (CNS), cardiovascular, gastrointestinal, genitourinary functioning, extrapyramidal and anticholinergic activity, diabetes, and prolactin-related SE. Patients rate the frequency of each SE and the level of distress it causes, with the total scale score derived from the sum of these frequencies. The Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale, a clinician-rated scale, is considered the gold standard for recording SE induced by psychotropic drugs (35, 156). The original UKU scale includes 48 items that assess the severity of SE, with severity ratings ranging from 0 (no side effects) to 3 (marked side effects). For this study, the GASS items were matched with the UKU items, and additional items on nocturnal enuresis and breast pain were included as per the manual's suggestion. The procedure followed the Danish validation approach (35), with the same timeframe for GASS questions as the UKU ones, and the total scale score was calculated by summing the matched individual items. The WHO Disability Assessment Schedule (WHO-DAS) 2.0 is a generic self-rated instrument for measuring health and disability levels (255) . The brief version, which contains 12 items and has been validated for patients with psychosis (256), was used in this study. It asks about the level of difficulty in performing daily activities over the past 30 days, with scores indicating the extent of functional impairment. The EuroQoL-5 dimensions-5 levels (EQ-5D-5L) is a tool for screening quality of life (118). It comprises two parts: five Likert five-level questions about various aspects of health and a visual analog scale (VAS) for patients to rate their perceived health. For this

work, only the VAS was considered due to its simplicity and relevance for patients with schizophrenia (257).

Translation and Validation Procedure

The translation of the Glasgow Antipsychotic Side-effect Scale (GASS) into Italian adhered to established guidelines in the literature (258). The process began with obtaining permission from the scale's creator, Prof. M. Taylor, for the Italian translation. An Italian clinician proficient in English and an English native-speaking translator independently translated the scale into Italian. With input from five patients, the two versions were combined into a single Italian version. Subsequently, a native English-speaking clinician fluent in Italian and an Italian native-speaking translator back-translated the Italian version into English. The back-translated version was then consolidated by consensus. The final back-translated documents were reviewed by the GASS creator to ensure consistency with the original scale. Upon receiving approval, the translated scale was tested with 10 patients to confirm its usability.

Raters

In this study, the self-rated questionnaires were administered by three senior psychiatrists and three psychiatrists in training at the Psychiatry Unit. To enhance inter-rater reliability for the UKU Side Effect Rating Scale, the senior and in-training psychiatrists conducted a preliminary assessment on 10 patients before administering the scale for the study.

Statistical Analysis

Structural Validity and Internal Consistency

The Glasgow Antipsychotic Side-effect Scale (GASS) is a comprehensive scale that assesses the burden of side effects (SE) associated with antipsychotic (AP) drugs. Although the GASS was originally designed without subscales, using a total score derived from summing all item scores, the study conducted a confirmatory factor analysis (CFA) to evaluate the original one-factor construct of the scale. The CFA used diagonally weighted least squares (DWLS) estimation due to the ordinal nature of the item ratings. The fit of the CFA model was assessed using several indicators: the chi-squared test, the comparative fit index (CFI; indicating a good fit when $\geq$ 0.95), the Tucker–Lewis index (TLI; indicating a good fit when TLI $\geq$ 0.95),

and the root-mean-square error of approximation (RMSEA) with its 90% confidence intervals (CI; indicating a good fit when <0.06) (259). The model was considered for modification by adding error covariances based on modification indices that could significantly improve the model's fit. Internal consistency was evaluated by calculating Cronbach's alpha and its 95% CI, with a value of ≥ 0.7 indicating good internal consistency (260). Inter-item Spearman's rho correlations were also examined, with an average inter-item correlation between 0.2 and 0.4 suggesting good internal consistency (261).

Concurrent Criterion Validity

The study assessed the agreement between the Glasgow Antipsychotic Side-effect Scale (GASS) and the Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale, which is considered the gold standard (35). Key metrics such as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using the UKU items as the reference standard. Additionally, phi coefficients of association between the dichotomized GASS and UKU items were computed to provide a measure of concurrent criterion validity between the scales (262). The phi value was then interpreted using Rea and Parker's anchor points (263) to gauge the strength of the association. The relationship between the total scores of the GASS and UKU was also examined using Spearman's rho (ρ), with a rho value of ≥ 0.7 indicating good agreement between the scales (260). This analysis aimed to determine how well the GASS corresponds with the UKU in measuring the side effects experienced by patients on antipsychotic medication.

Hypothesis Testing for Construct Validity

The study evaluated the construct validity of the Glasgow Antipsychotic Side-effect Scale (GASS) by examining its relationship with functional impairment, as measured by the WHO Disability Assessment Schedule (WHO-DAS) 2.0, and perceived quality of life, as measured by the EuroQoL-5 dimensions-5 levels (EQ-5D-5L) Visual Analog Scale (VAS). This was done using Spearman's rho (ρ), with good construct validity indicated by an absolute rho value of 0.5 or greater (264). Additionally, the relationship between the frequency and distress scores of individual GASS items was assessed using Spearman's rho. The study also explored differences in the GASS total score across various patient subgroups, such as sex, diagnosis,

and employment status, using the Mann–Whitney U test. Correlations between the GASS total score and demographic as well as illness-related variables were investigated.

Clinical Feasibility

In terms of clinical feasibility, the time taken to administer the GASS, and any questions participants asked clinicians while completing the questionnaire were recorded. The analyses were conducted using the caret (265), psych (266), and lavaan (267) packages with the RStudio IDE (integrated development environment) (268).

Results

In the study, 111 participants were recruited, and complete data were obtained from 100 individuals for the Glasgow Antipsychotic Side-effect Scale (GASS) frequency items, and from 81 for the distress section. The median age of the sample was 47 years, predominantly male (61%), and the majority had high school education. Most participants were unmarried (72%), unemployed (75%), and evenly split between smokers and non-smokers.

The population had a variety of comorbidities, including dysthyroidism, diabetes, hypertension, and hypercholesterolemia. The median GASS total score was 13, suggesting moderate side effects, while the UKU side effect rating scale average was 6. Participants had been living with their illness for a median duration of 13 years and had a median of 2 lifetime hospitalizations. Treatment typically involved second-generation antipsychotics with a median olanzapine equivalent dose of 12.33 milligrams. The most prescribed medications were paliperidone, olanzapine, aripiprazole, and risperidone. Monotherapy was more prevalent than polypharmacy, and most participants (90%) were being treated as outpatients. Mood stabilizers, antidepressants, and benzodiazepines were concurrently used by about half of the sample.

A confirmatory factor analysis (CFA) did not support the original one-factor construct of GASS, prompting a model re-specification that improved fit (chi-squared = 247.14, df = 184, p-value = 0.001; CFI = 0.90; TLI = 0.89; RMSEA = 0.059, 90%CI [0.038, 0.077]). Cronbach's alpha for the total score was 0.81, indicating good internal consistency, with an average inter-item correlation of 0.17.

Criterion validity was examined by comparing the GASS with the Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale, considered the gold standard (35). Sensitivity and specificity varied across items, with strong associations found for eleven items and moderate associations for six. A fair agreement was observed between the total scores of GASS and UKU (ρ = 0.67, p-value < 0.001).

Construct validity was supported by correlations between the GASS total score, and functional impairment measured by the WHO Disability Assessment Schedule (WHO-DAS) 2.0 (ρ = 0.45, $p < 0.001$) and perceived health measured by the VAS of EQ-5D-5L ($\rho = -0.4$, $p < 0.001$). The relationship between the frequency of side effects and the distress caused varied, with some side effects being more distressing when more frequent.

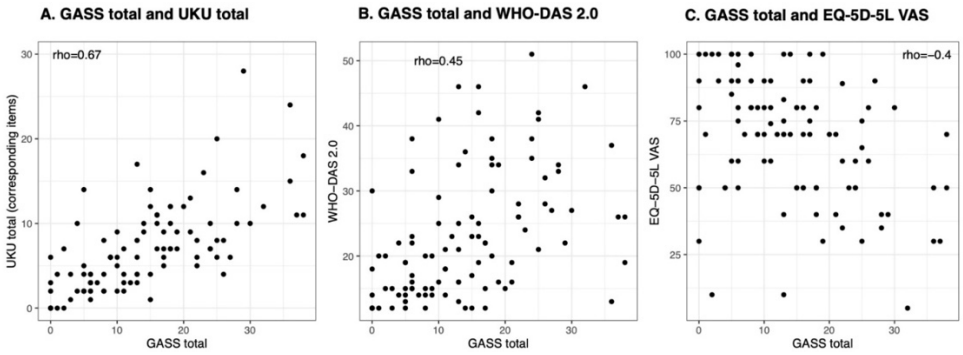

Figure D1. Correlations between the GASS total score and the UKU total score (a), the WHO-DAS 2.0 total score (b), and the EQ-5D-5L Visual Analogue Scale (c).

No significant differences in the GASS total score were found between patient subgroups, except for those who provided distress data. The GASS total score did not correlate with any continuous variables such as age or olanzapine equivalent dose.

Clinical feasibility was assessed by recording the median completion time for the GASS scale, which was 4:42 minutes. Some participants had difficulties understanding how to fill in the distress column.

Discussion

The study aimed to translate the Glasgow Antipsychotic Side-effect Scale (GASS) into Italian and validate it as a measure of the antipsychotic side-effect (AP-SE) burden. A total of 111 participants were recruited, with 100 providing complete data for the GASS frequency items. The sample included

patients with schizophrenia and bipolar spectrum disorders, predominantly treated with second-generation antipsychotics. The confirmatory factor analysis (CFA) initially did not support the one-factor construct of the GASS, but the fit improved when correlations between certain items were considered, particularly items 17 and 18, which were rare in the sample. This rarity was consistent with findings from the CATIE study (269). The GASS demonstrated fair sensitivity and specificity for most individual side effects when compared against the UKU scale, with sensitivity and specificity generally above 70%. While the positive predictive value (PPV) of the GASS items was relatively high, the negative predictive value (NPV) was not as robust, indicating that patients might not recognize the same side effects identified clinically by the UKU. Despite this, the primary aim of the GASS to measure SE distress was deemed acceptable. The correlation between GASS and UKU items ranged from negligible to strong, with 11 items showing strong or relatively strong associations. This discrepancy between symptoms identified by patients and clinicians may be due to patients' tendency to report symptoms that cause distress as present, even when clinicians recognize them as mild or absent (270). Construct validity was confirmed by an inverse correlation between the GASS total score and both functional impairment (measured by WHO-DAS 2.0) and quality of life (measured by EQ-5D-5L VAS). The frequency of side effects was proportional to the distress they caused, suggesting the GASS is better suited to estimate the SE burden rather than identify specific SE. The study adds to existing research on the GASS (35, 253, 254). maintaining good internal consistency. However, consistency with the gold standard (UKU) was not as satisfactory as in the Danish validation, although it was relatively robust for more than half of the items. The CFA indicated that the one-factor analysis did not fit well, suggesting the need for further exploratory factor analysis.

Limitations of the study include the impact of staff training on inter-rater reliability, the use of a slightly modified instrument from the original GASS, and the small number of events for certain side effects. The study did not measure the discriminative ability or test-retest reliability, and the sample characteristics may affect generalizability. Strengths of the research include a detailed analysis of the GASS, extending the generalizability of the results to

include inpatients. The validation followed current standards for translating scales and provided a pragmatic instrument to measure AP-SE distress, requiring only 5 minutes to complete, which was previously unavailable in a validated form for Italian patients with psychotic disorders. In conclusion, the Italian translation and validation of the GASS offer a valuable patient-reported outcome measure (PROM) that could benefit patients. Increased clinician attention to AP-SE may improve patients' quality of life and psychosocial functioning. However, clinicians should use the GASS as a screening tool alongside a clinical interview, rather than as a standalone diagnostic tool.

Glasgow Antipsychotic Side-Effect Scale (GASS)

Nome: Età: Genere: M/F

Cortesemente, elenca qui sotto i farmaci che assumi e i dosaggi giornalieri:

Il presente questionario fa riferimento a come ti sei sentito di recente. In particolare, viene utilizzato per sapere se hai degli effetti collaterali derivati dall'uso dei farmaci antipsicotici.

Cortesemente, metti una crocetta nella colonna che meglio indica la frequenza con cui hai sperimentato i seguenti effetti collaterali. Inoltre, qualora sia andato incontro a uno di questi effetti collaterali, riporta nell'ultima colonna un numero da 1 a 10 che indichi quanto questo ti abbia recato fastidio.

Nel corso dell'ultima settimana	**Mai**	**Ona volta**	**Qualche volta**	**Ogni giorno**	**Livello di fastidio 1 = per niente 10 = molto**
1. Mi sono sentito assonnato durante il giorno					
2. Mi sono sentito come drogato o come uno zombie					
3. Ho avuto le vertigini quando mi sono alzato in piedi e/o sono svenuto					
4. Ho sentito il mio cuore battere in maniera irregolare o insolitamente veloce					
5. I miei muscoli erano tesi o sono andati incontro a contrazioni					
6. Ho avuto tremore alle mani o alle braccia					
7. Le mie gambe non riuscivano a stare ferme e/o io non riuscivo a restare seduto					
8. Mi è capitato di sbavare					
9. I miei movimenti o il mio modo di camminare sono stati più lenti del solito					
10. Ho avuto movimenti incontrollabili della faccia o del corpo					
11. Ho avuto la visione offuscata					
12. Ho avuto la bocca secca					
13. Ho avuto difficoltà a urinare					
14. Ho avuto la sensazione di sentirmi male oppure ho vomitato					
15. Ho bagnato il letto					
16. Ho avuto molta sete e/o ho urinato spesso					
17. Le zone attorno ai miei capezzoli sono state doloranti e gonfie					
18. Ho notato la fuoriuscita di liquido dai miei capezzoli					
19. Ho avuto difficoltà nel provare piacere nel sesso					
20. Solo uomini: ho avuto difficoltà a raggiungere l'erezione					
Mettere una crocetta su "Si" o "No" in riferimento agli ultimi <u>tre mesi</u>	**No**		**Si**		**Livello di fastidio 1 = per niente 10 = molto**
21. Solo donne: ho notato dei cambiamenti nel mio ciclo mestruale					
22. Uomini e donne: ho preso peso					

Figure D2: Italian Version of the Glasgow Antipsychotic Side Effect Scale

Developing PROTECTS-SE: A Qualitative Usability Study of a Novel Patient-Reported Outcomes Tool for Managing Side Effects in Shared Decision-Making in Schizophrenia Spectrum Disorder Care

The ensuing section provides a detailed summary of the publication under peer review.

Introduction

Schizophrenia, a multifaceted and chronic mental illness, is distinguished by both positive symptoms, such as hallucinations, and negative symptoms, like a lack of motivation. The primary treatment involves antipsychotic drugs (41), which, despite their effectiveness, often result in significant side effects. These affect up to 75% of patients(271), potentially influencing treatment adherence (272) and life quality (273). Critical aspect of psychiatric care is managing these side effects, aiming to balance efficacy and tolerability. Strategies include maintaining minimum effective doses of antipsychotics, though this can increase the risk of relapse (23). Decision-making regarding dose adjustment or alternative therapies, such as medication switching, usually depends on clinical judgment (274) and is better guided by evidence-based approaches, potentially supported by digital health tools (275). In the context of healthcare, DDAs are emerging as pivotal in decision-making. These tools provide patients with comprehensive, evidence-based information on their condition and treatment choices, fostering informed collaboration with clinicians (276). Effective DDAs integrate current evidence, personalization, and simplification of scientific data for patient comprehension (277). They also encourage transparent decision-making, shifting from paternalistic to participatory shared decision-making (SDM) models (278). The PROTECTS-SE app, specifically designed for managing medication side effects in schizophrenia, exemplifies the integration of SDM and patient-centered care. It empowers patients to track their health and medication knowledge, providing accessible, evidence-based drug information. For clinicians, it offers patient-reported data, facilitating timely, individualized medication adjustments. This app includes features like a comprehensive medication guide, antipsychotic information, drug interactions, side effects, and management strategies. While the Shared-Decision Making Assistant (SDMA) focuses on selecting antipsychotics in acute settings(279), PROTECTS-SE caters to stable patients managing

antipsychotic side effects. It shares SDMA's goal of aiding informed pharmacological decisions but is uniquely tailored for long-term management. This study presents the PROTECTS-SE app as a sophisticated tool in schizophrenia management, detailing its features, theoretical underpinnings, and insights from usability tests and interviews with patients and clinicians. The analysis, conducted using a qualitative framework, centers on aspects such as ease of use, clarity of information, meeting user needs, enhancing patient-physician collaboration, improving treatment adherence, empowering patients, and providing clinician utility.

Methods

PROTECTS-SE, a web-based tool for schizophrenia management, was developed in line with the International Patient Decision Aid Standards (IPDASi) v4.0 (280). This paper details the tool's development and its evaluation through user testing, including interviews with patients and clinicians, with approval from the Internal Ethic Review Board of Psychology Research – IERB.

PROTECTS-SE Development

The application, optimized for local storage on Windows™ systems, ensures data protection through a secure physician login (Figure E1). Physicians input patient demographics and medication details (Figure E2), identifying the primary antipsychotic using the Defined Daily Dose (DDD) method (90). Patients assess side effects using the Italian version of the Glasgow Antipsychotic Side-effect Scale (GASS) (34, 49) and select up to three significant side effects (Figure E3), guiding the app's recommendations. PROTECTS-SE presents data in three sections (Figure E4): clinical investigations, pharmacological interactions (linked to the DrugBank website) (281), and interventions like dose adjustments or medication switches. This information is consistent with English-language guidelines from various countries, excluding Italian guidelines due to their lower standard (282) The app provides a table format in the "Possible Interventions" section, showing guideline recommendations for each intervention-side effect combination. Key features include a dose reduction page with a graph estimating relapse risk based on dose changes (111) (Figure E5), and a

medication switch page with forest plots from network meta-analyses for visual comparison (42, 283-286) (Figure E6). Following feedback from initial interviews, a semi-quantitative dynamic table was introduced for simpler presentation of medication effectiveness on selected side effects.

User-testing study

We followed the COREQ guideline for reporting qualitative research (287)

Personnel Characteristics and Relationship with participants

Interviews were carried out by psychiatry specialists and third-year psychiatric residents (AR, ADF, and PCu), supervised by a seasoned clinical psychology researcher and psychotherapist (PCa). The interviewers, unfamiliar to the patients, were introduced by their treating psychiatrists. Clinician participants were selected among colleagues familiar with the tool's development. The sample size adhered to Creswell's guidelines (288).

Theoretical framework

The study adopted a qualitative descriptive approach with thematic analysis, guided by Jakob Nielsen's usability dimensions and an added focus on psychological impact. This approach explored not only the app's operational aspects but also its influence on mental well-being and attitudes towards treatment adherence (289).

Participant selection and Setting

Participants for the PROTECTS-SE study were selected using purposive sampling, targeting adults over 18 years with stable schizophrenia spectrum disorders, following DSM-5-TR criteria. Exclusion criteria limited participation to outpatients, excluding inpatients to focus on those in a stable chronic phase. A total of 30 participants, including both patients and clinicians (specialists and residents), were selected, with no refusals to participate. Interviews were conducted at Policlinico Gaspare Rodolico Hospital and Oasi Regina Pacis mental health center in Catania, as well as some clinicians' workplaces. This varied setting was chosen to ensure comfort

and convenience for participants, facilitating open discussion. The data collection period extended from June to October 2023.

Data collection

Interviews for both clinicians and patients began by collecting sociodemographic data. The data collection process involved sociodemographic questionnaires, with tailored interviews for patients and clinicians. Questions covered app usability, learning ease, and its role in therapeutic decision-making. Interviews lasted 30 to 45 minutes and were transcribed using OpenAI Whisper ASR (290).

Data analysis

Data coding and analysis were performed by the interviewers, following Braun and Clarke's thematic analysis method (291). The analysis involved double coding, team review, and grouping themes within predefined macro-areas using Excel. Key demographic details were included alongside identifiers in the results section.

Results

Participants

In the study, 30 interviews were conducted, comprising 16 patients and 14 clinicians. The clinicians included both specialists and residents: specialists averaged 50 years of age with 5 to 35 years of experience, primarily working in hospitals or mental health centers, while residents were around 32 years old with 1 to 4 years of experience in hospital training. On average, these physicians manage about 22.64 schizophrenia patients per month. Their expertise varied, with a nearly equal distribution among high, moderate, and less experienced groups. A significant majority (92.86%) believe that decision aids improve clinical decision-making, and 71.43% report better communication with patients. Patient participants were predominantly male (75%), averaging 40 years old, and mostly held high school education. They had been under specialist care for an average of 10 years, with many having undergone therapy changes within the last year. Their digital device familiarity scored 6.44 out of 10, indicating moderate comfort with technology. Notably, a high percentage (92.86%) were aware of their medications' purposes, reflecting a potential readiness to engage with electronic decision aids.

Qualitative Analysis

The qualitative analysis of participant perspectives yielded five distinct categories with multiple themes.

Dynamics of the Doctor-Patient Relationship and Involvement in Decisions

Patients' perspectives

The thematic analysis highlighted diverse attitudes among patients towards their involvement in clinical decision-making. A group of six patients demonstrated an active approach, transitioning from passively following prescriptions to engaging in dialogues and making joint decisions with their providers. This indicates a preference for collaborative decision-making, as exemplified by Pt08 (50, M, Ther. Assisted Comm., Primary Sch.), who valued the opportunity for involvement. However, a tendency to defer to medical authority was also noted, as seen in Pt10 (42, M, Hosp., High Sch.) and Pt11 (57, M, Hosp., Middle Sch.), who expressed strong trust in their doctors' recommendations.

Another theme was the varying attitudes toward communication with clinicians. Some patients reported positive experiences in discussing therapies, feeling acknowledged and valued, like Pt14 (44, F, Ther. Assisted Comm., High Sch.), who appreciated the personal care in these interactions. Contrarily, other patients rarely discussed health information independently found online with their doctors, indicating limited dialogue but still expressing satisfaction with their level of involvement in treatment decisions.

Clinicians' perspectives

Clinician perspectives were categorized into three themes: their prescriptive approach, addressing patient needs, and patient engagement outside direct clinical interactions. Some clinicians, especially in acute psychiatric settings, showed a paternalistic approach with minimal patient discussion about treatment options. Med01 (52, F, Spec., Hosp., 27) and Med02 (36, M, Spec., Ther. Assisted Comm., 5) indicated that patient involvement in decision-making typically begins after initial stabilization. Med11 (44, M, Spec., Mental Health Ctr., 15) emphasized the importance of patient insight in decision-making, though also expressed concerns about patients' requests potentially reflecting a non-acceptance of therapy. Regarding shared decision-making (SDM), clinicians acknowledged the importance of

involving patients and their families in strengthening the therapeutic alliance. However, there was also an awareness of the challenges posed by patients discussing online health information, with Med02 (36, M, Spec., Ther. Assisted Comm., 5) noting that such information is often irrelevant. Med14 (37, F, Spec., Mental Health Ctr., 10) observed age-related differences in how patients engage with online information, while Med13 (30, F, Res., Hosp., 3) pointed out that patients may selectively disclose concerns developed from online sources.

The App in the Management of Treatment and Side Effects

Patients' perspectives

Patients showed varied opinions about PROTECTS-SE's utility in treatment management and side effects. Some, like Pt02 (30, F, Hosp., Univ.), believed the app could enhance trust and compliance in medical decisions, citing its ability to compare medications and streamline the treatment process. Pt14 (44, F, Ther. Assisted Comm., High Sch.) appreciated the app's facilitation of immediate doctor-patient engagement, enhancing the connection beyond regular visits. The app's role in promoting patient autonomy and motivation was a prominent theme. It was seen as helpful for pre-appointment preparation and increasing awareness of side effects, with patients like Pt04 (37, M, Hosp., High Sch.) recognizing its value in understanding medication importance. However, some expressed skepticism about its ability to truly enhance autonomy, with Pt06 (60, M, Hosp., Middle Sch.) doubting additional benefits beyond their existing doctor relationship, and Pt04 (37, M, Hosp., High Sch.) questioning the reality of autonomy given the need for doctor approval. Concerns about potential misunderstandings due to the app's use were raised. Pt16 (45, M, Ther. Assisted Comm., High Sch.) pointed out that the app might lead to misaligned expectations between patients and medical advice, particularly in medication adjustments.

Clinicians' perspectives

Clinicians acknowledged the PROTECTS-SE app's dual role in enhancing patient involvement and aiding therapeutic decision-making. Its efficiency in identifying side effects and suggesting treatment strategies was noted, with Med03 (50, M, Spec., Hosp., 24) open to its potential influence on prescribing practices. The app was also seen as valuable for SDM, providing clear,

scientific information for both doctors and patients. Med07 (30, F, Res., Hosp., 2) emphasized its role in building trust by saving patients from confusing searches and assuring them of evidence-based decisions. Clinicians like Med14 (37, F, Spec., Mental Health Ctr., 10) appreciated features such as DrugBank™ for checking drug interactions, enhancing mutual trust in the therapeutic alliance. While the psychological benefits of the app were highlighted, some clinicians expressed reservations. Concerns included information overload for patients (Med01, 52, F, Spec., Hosp., 27) and the risk of alarming content (Med09, 34, M, Res., Hosp., 1). Risks of misinterpretation and over-reliance on the app for medication changes were noted by Med13 (30, F, Res., Hosp., 3) and Med14 (37, F, Spec., Mental Health Ctr., 10). Med11 (44, M, Spec., Mental Health Ctr., 15) advocated for selective app use, emphasizing its potential to improve clinical outcomes when used appropriately. In summary, while clinicians generally did not express concerns about misunderstandings, they emphasized the need to balance the app's use with clinical judgment and the integrity of the doctor-patient relationship.

Feedback: UX/UI

Patients' perspectives

Patients largely reported a positive experience with the app's user interface (UI) and usability. They found it straightforward, simple, and easy to use, with an intuitive design and clear instructions. The app's simplicity and colorful design were frequently praised. While navigation between screens was mostly easy, some patients found exploring alternative medications more complex than selecting side effects. Most patients felt confident about using the app after a break, indicating its user-friendly and memorable design. However, a few, like Pt11 (57, M, Hosp., Middle Sch.) and Pt16 (45, M, Ther. Assisted Comm., High Sch.), struggled with concentration and memorization. Suggestions for UI improvements included more vibrant colors, color-coding for individual drugs, and larger text for better readability. A few patients expressed the need for improvements in the UI. Pt02 (30, F, Hosp., Univ.) called for more vibrant colors, and Pt14 (44, F, Ther. Assisted Comm., High Sch.) suggested color-coding for individual drugs within forest plots to enhance the visual appeal and distinctiveness. Pt05 (30, M, Hosp., High Sch.)

and Pt07 (33, M, Ther. Assisted Comm., High Sch.) wanted larger text to improve readability.

Clinicians' perspectives

Clinicians were generally satisfied with the app's functionalities, finding the processes not overly complicated or lengthy. They praised its simplicity and information richness. Some clinicians experienced difficulties with certain functionalities and desired more clarity. Most felt confident in using the app after a period of non-use, though a few anticipated needing re-familiarization. Suggestions for UI improvements focused on making certain clickable elements more intuitive and integrating drug interaction information more seamlessly.

Feedback: Data Visualization (Graphs vs. Tables)

Patients' perspectives

About one third of patients preferred graphical representations (forest plots) for understanding medication changes, finding them easy to understand, like Pt14 (44, F, Ther. Assisted Comm., High Sch.). Others favored descriptive tables for their clear data presentation. Pt06 (60, M, Hosp., Middle Sch.) and Pt02 (30, F, Hosp., Univ.) found tables more accessible, especially for those less comfortable with mathematical data.

Clinicians' perspectives

Some clinicians found graphical representations straightforward, but the majority preferred descriptive tables for their ease of understanding and visual orientation. They suggested making sections on medication switches more user-friendly and retaining both formats for their respective strengths.

Feedback: New Features

Patients' perspectives

Patients proposed new features like a journaling function for recording daily mental states, inclusion of brand names in the drug reference system, a feature for reporting adverse reactions, and a mobile version of the tool.

Clinicians' perspectives

Clinicians suggested additional features, including a bookmarking option for significant therapeutic decisions, detailed information on relapses, guidance for implementing medication switches, inclusion of depot formulations, more comprehensive information on combining medications, capability to gather

biometric parameters, and a mobile version of the tool for increased accessibility.

Discussion

Our study explored the application of PROTECTS-SE, a novel shared decision-making (SDM) tool, assessing its utility and impact in a clinical setting. The findings reveal a spectrum of clinician approaches to SDM, from paternalistic to more patient-inclusive, particularly after patients have stabilized. Patients demonstrated a mix of enthusiasm for involvement and a tendency towards passive reliance on clinician judgment. PROTECTS-SE, primarily an SDM facilitator, was also recognized for its broader clinical management benefits, with users acknowledging its potential for minimizing misunderstandings, albeit with some concerns about possible misuse.

The user experience of PROTECTS-SE was largely positive, aligning with Nielsen and Molich's usability standards in terms of learnability, efficiency, and memorability. Patients reported feeling more engaged in their therapy, and clinicians appreciated the tool's adherence to clinical guidelines. The data visualization aspect, featuring both forest plots and tables, presented a learning curve for some users, indicating a need for more user-friendly or alternative graphical representations to improve comprehension and accessibility.

Suggestions for enhancements included the addition of brand drug names and depot formulations, a journaling feature, bookmarking options, detailed guidance on switching antipsychotics, and developing a mobile version. The feedback highlighted the potential for the tool's application beyond the initially intended inpatient settings, with both clinicians and patients recognizing the value of a mobile version.

The study's limitations included the possibility that the semi-structured interview format might have limited the emergence of deeper insights, and the relatively short duration of patient interviews due to the distress experienced by some participants. Additionally, the generalizability of the findings is limited to stable patients, and experiences of depot patients, who may face unique challenges, were not distinctly analyzed. The psychiatrist responses could also have been influenced by social desirability bias,

reflecting a preference for portraying a more collaborative approach in patient care.

In conclusion, PROTECTS-SE demonstrates promise as an effective tool in enhancing patient empowerment and communication in healthcare settings, resonating with the growing trend of digital health tools in patient-centered care. The study provides valuable insights for future development and research, emphasizing the importance of user-friendly design and the potential benefits of expanding the tool's features and accessibility.

Figure E1: PORTECTS-SE login page

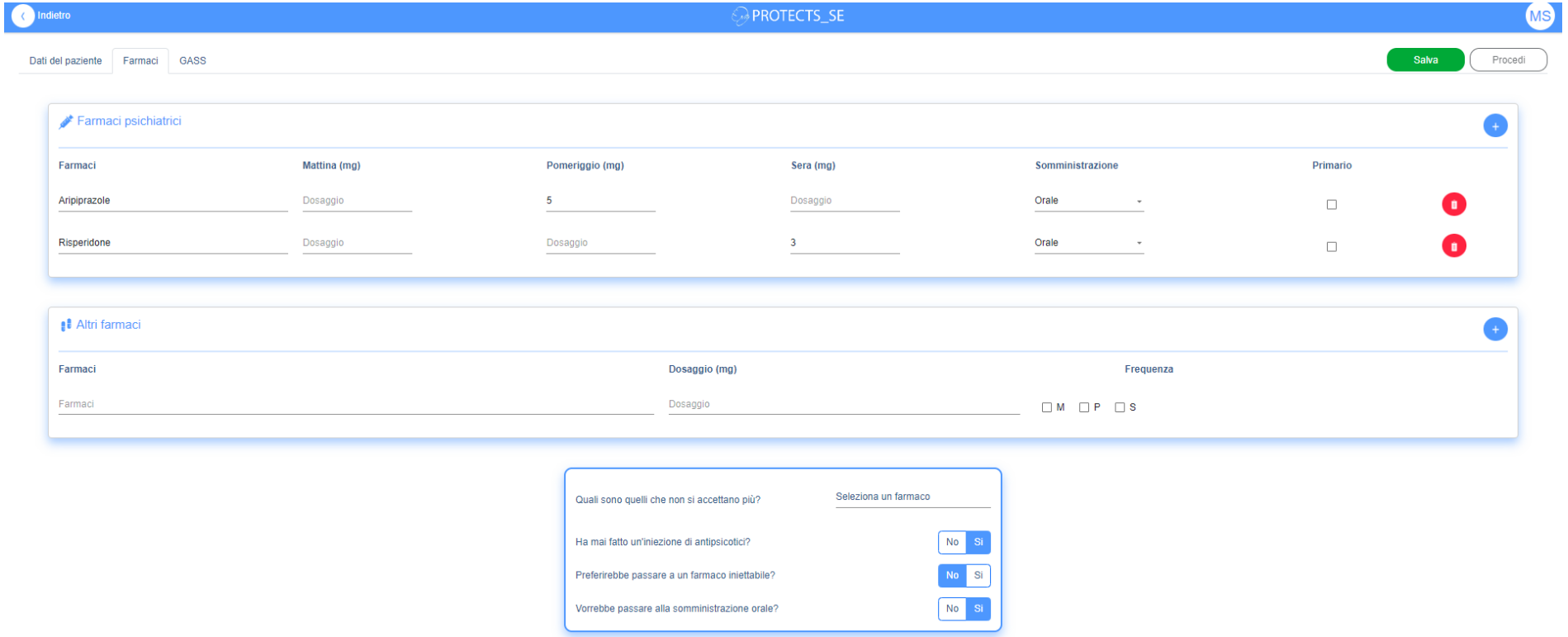

Figure E2: PROTECTS-SE drugs annotation page

Figure E3: PROTECTS-SE antipsychotics side effect selection page

Figure E4: PROTECTS-SE overview of possible guidelines recommendations page

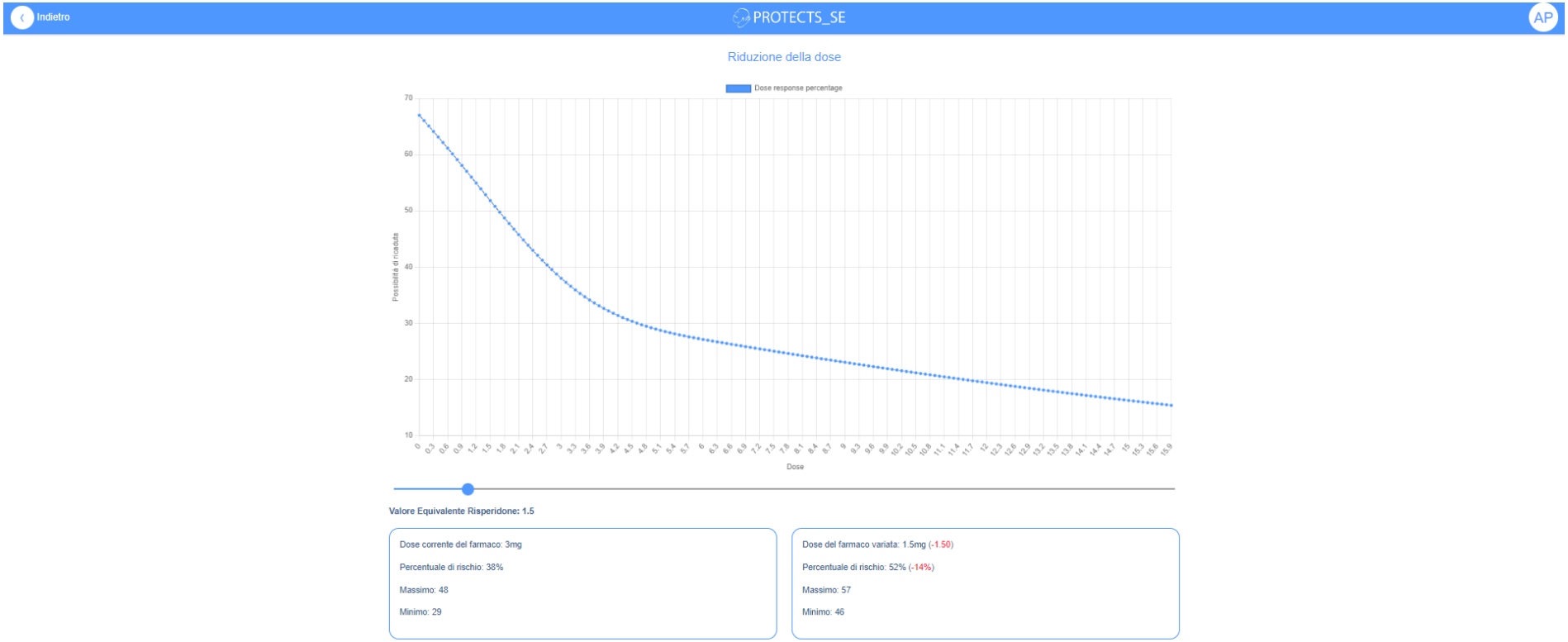

Figure E5: Antipsychotics dose-response relapse risk graph

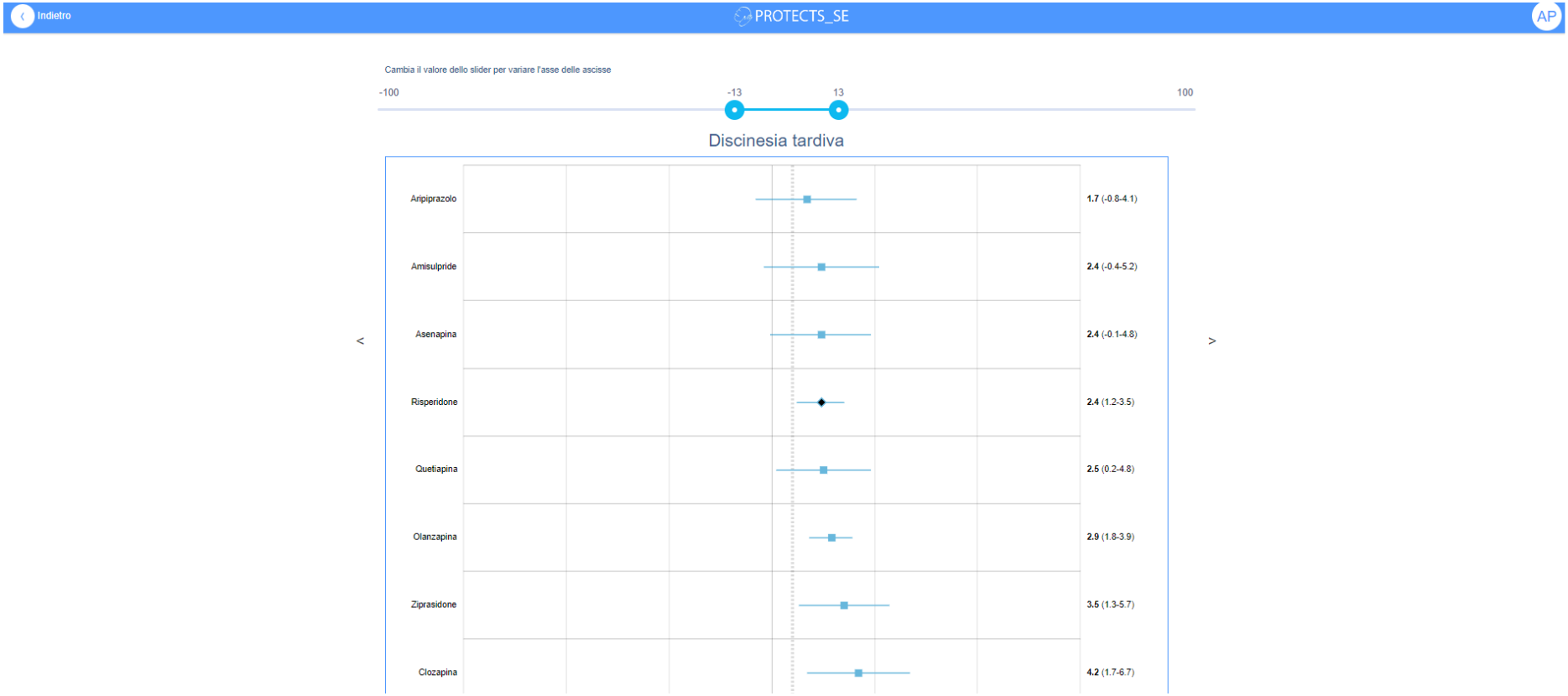

Figure E6: forest plot graph

General discussion

My original project aimed to develop a Shared Decision-Making (SDM) tool to help patients and clinicians reduce the antipsychotic dose. However, the data I collected and the evidence from recent publications discouraged this narrow focus. As a result, the final app, PROTECTS-SE, is an SDM tool that presents the most rigorously redacted guidelines for addressing antipsychotic side effects to the patient-clinician dyad. Here, I will discuss the steps that led me from the original plan to the final product.

Primarily, data emerging from the Cochrane systematic reviews have significantly scaled down the original objective of developing a tool aimed at reducing antipsychotic dosage (23). Indeed, out of 22 studies that yielded data useful for meta-analyses, it is evident that subjects undergoing dosage reduction more frequently experience relapses and are more likely to drop out of the study due to side effects or for any reason, without this leading to an improvement in quality of life or functioning. However, it should be noted that some side effects do show marginal improvement, namely movement disorders or weight gain. Nonetheless, the data are still too sparse to allow for adequate generalization. Moreover, similar results have been highlighted by the review on the reduction of polypharmacy, although the scarcity of studies included, specifically only 5, makes the generalizability of these results even more complicated. Additionally, the recent Network Meta-Analysis by Ostuzzi and colleagues indicates that switching antipsychotics is safer for patients with schizophrenia than dose reduction (22). In light of these evidence-based findings, the work has focused on developing a Digital Decision Aid aimed not only at considering dose reduction but also other procedures to optimize the clinical status of patients experiencing side effects from antipsychotics. To this end, we have delved into the literature data about other Decision Aids for schizophrenia and found that as of May 2021, only 6 of these were available (277). Specifically, 5 were digital (229, 232-234, 236) and 1 was paper based (235). Many of these have been evaluated through feasibility studies, and only 2 have produced data from randomized clinical trials (229, 232). The analysis of these tools was not aimed at evaluating their quality per se, but at identifying the essential elements that a Digital Decision Aid for schizophrenia should have. For this reason, we focused on 3 essential

elements to be considered in the development of these devices. Namely, the source of evidence, particularly from where the evidence data are drawn. Secondly, the ability of these tools to combine evidence data with the values, needs, and requirements of the patients. And finally, the way these tools should present the information. Regarding the first point, only one study exclusively adopted sources representing the highest level of evidence, namely a Network Meta-Analysis (236). The other studies, however, employed combined and heterogeneous approaches, integrating not necessarily in a systematic evaluation of literature sources, both meta-analytic data and observational data. Another significant aspect emerging in the development of these tools is the difficulty in producing an information source that meets the patient's characteristics (240). In this regard, tools have been developed that include the use of algorithms to generate recommendations tailored to the patient's characteristics once their demographic data have been collected. However, this approach paradoxically distances the patient because it produces tools that potentially define a single pathway, which might theoretically be the best for the patient but do not necessarily align with patients' values. Therefore, in the attempt to develop devices that reduce the paternalistic dimension of the doctor, they themselves become a tool of a paternalistic approach and not of shared decision-making. Thus, another essential element that emerges from this investigation is that it is useful to collect and present data in a manner as comprehensible as possible for both doctor and patient, but the choice should be left to them in the context of the medical consultation. To conclude, a third significant point is the way data are presented by these tools. Some tend to present various possible options, allowing for doctor-patient dialogue, while others opt for a hierarchy of intervention options, implicitly reducing the opportunity for discussion about intervention options as priority is inevitably given to certain approaches over others. Moreover, another important element regarding the presentation of data is the volume of information presented. It must be considered that patients may have difficulty processing information, and thus should not be overwhelmed. For this reason, we have suggested that the devices be calibrated to present a variable amount of information based on the patient's education level and his cognitive function. In light of the above considerations

and the evolution of the literature data, as previously mentioned, we have directed our work towards the development of a Digital Decision Aid aimed at presenting recommendations derived from guidelines in the case of side effects. With this purpose in mind, we deemed it essential to include in the tool a Patient Reported Outcome measure relevant to side effects. Among the available tools, we identified the Glasgow Antipsychotics Side Effects Scale (34), abbreviated as GASS, for two main reasons: the absence of other self-administered tools in the Italian language, and secondly because we recognized this questionnaire as not only the gold standard for this purpose but also as characterized by considerable ease of use (30). We translated the GASS in Italian language and administered it to 100 patients, of which about two-thirds were affected by schizophrenia spectrum disorders and the remainder by bipolar spectrum disorders (49). Subsequently, we carried out analyses of structural validity, internal consistency, concurrent criterion validity, and construct validity, and also evaluated its clinical feasibility. Particularly in concurrent criterion validity, we compared the tool with the UKU scale (156), considered the gold standard for collecting side effects data by the clinician. Overall, our data indicate that the tool is valid in measuring the burden related to side effects and as a screening instrument for specific side effects, which should obviously be accompanied by a clinical review (49). The Italian translation of this tool has allowed its integration into the Digital Decision Aid we developed, thereby ensuring that the patient can directly present their own treatment needs and the side effects that most disturb them. Aware of the data gleaned from the reviews and equipped with a self-administered tool for assessing side effects in Italian, we proceeded to develop an app named PROTECTS-SE, designed to collect these side effects, and suggest, within a framework of shared decision-making, the optimal treatment options according to guidelines. Subsequently, a usability study of the tool was conducted, presenting it to 16 patients and 14 clinicians. Overall, it was well-received by both groups, although it should be emphasized that there remains a certain reluctance among doctors who work with patients in acute states to use devices for shared decision-making, and they typically show greater openness to their use only when the patient is sufficiently stabilized. From the data obtained, this tool, originally conceived to facilitate

dialogue between doctor and patient in the context of shared decision-making, is also suggested as a valid device to support clinician choices independently of its use in a shared approach. Of course, there were patients and clinicians wary of using such a tool, both for potential distortions and manipulations in the doctor-patient relationship and for the actual ability of the device to improve treatment adherence. Regarding the graphic interface and user experience, patients and clinicians predominantly expressed good comments; however, they requested larger and more readable text. Considering that both forest plots and a semi-quantitative tabular representation of the data were presented to the patients, the majority of participants, regardless of group, expressed a preference for the tabular mode, suggesting that forest plots can make it difficult to deeply understand the information presented. Finally, new features were suggested that have stimulated future developments of the device, foremost among them, requested by both groups, a mobile smartphone conversion of the tool and other minor additions.

Concluding remarks

My PhD project transitioned from developing a tool for antipsychotic dose reduction to creating PROTECTS-SE, a Shared Decision-Making (SDM) app addressing antipsychotic side effects. This shift was guided by Cochrane reviews and other studies indicating that dose reduction often led to relapses and didn't improve quality of life, with some marginal improvements in side effects like movement disorders and weight gain. Considering the scarcity of data and the safer alternative of switching antipsychotics, the focus shifted to a broader approach in managing side effects.

Reviewing existing Decision Aids for schizophrenia, we identified three key aspects for our tool: evidence-based sources, patient-specific recommendations, and clear presentation of information. The Glasgow Antipsychotics Side Effects Scale (GASS) was chosen for its ease of use and validity, and after translation and validation in Italian, it was integrated into PROTECTS-SE. The app was tested with patients and clinicians, showing positive reception but also revealing hesitance among doctors working with acutely ill patients. Feedback led to interface improvements and future development plans, including a mobile version.

In summary, the project evolved from a specific focus on dose reduction to a comprehensive tool for managing antipsychotic side effects, aligned with evidence-based guidelines and patient preferences.

This project is characterized by strengths and limitations. Among its strengths, it should be noted that the evidence collected has a systematic nature, and the evolution of the project has followed a rational approach, oriented towards the generation of a product with potential clinical utility. While guidelines commonly suggest dose reduction as a solution for managing side effects, this intervention cannot always be considered a safe option for the patient. Therefore, limiting the tool to that single option would have made it clinically less versatile and potentially at risk of being underused. Instead, our approach has enabled the production of a tool that clinicians and patients found useful, interesting, and user-friendly, leading us to believe that we have enriched the array of digital decision aids for schizophrenia. While our work has established the usability of the tool, its utility in clinical practice still needs to be assessed, which we aim to explore further.

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