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REVIEW ARTICLE

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Medication management of antipsychotic treatment in schizophrenia—A narrative review

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Abstract

Background/Objective: The risk-benefit ratio of antipsychotics in schizophrenia depends primarily on their effect on brain chemistry. An important factor influencing the efficacy of prescribed drugs is medication management, which can be defined as an ongoing process to manage and monitor the recommended use of antipsychotics to facilitate their cost-effective, adherent, and acceptable use.

Materials: We reviewed narratively relevant literature that examined the medication management of antipsychotics in schizophrenia based on a search of PubMed, Scopus, Web of Science, PsycARTICLES, and Cochrane in May 2020. We also included controlled interventional studies with a follow-up period of at least 2 years.

Result: Based on the previous literature, there is no unified approach for optimal medication management, but multiple useful strategies are presented for individual patients, prescribers, and organizations.

Conclusions: Systematic medication management may improve the risk-benefit balance of antipsychotics by achieving the lowest effective dose, minimizing adverse effects, and improving adherence. There is a need for well-designed naturalistic studies and clinical trials to optimize management in schizophrenia.

KEYWORDS
antipsychotic medication, medication management, risk-benefit ratio, schizophrenia

1 | BACKGROUND

Medication management is defined as a process to implement physicians' recommended use of medications, aiming to facilitate their safe and effective use and optimal therapeutic outcomes (Howard et al., 2009). Insufficient or absent antipsychotic medication management is common. Weinmann, Janssen, and Gaebel (2005) found that 73% of individuals with persistent psychotic symptoms received insufficient antipsychotic drug management. Nykänen et al., (2016) reported that 33% of schizophrenia subjects using antipsychotics did not have any treatment contact. In particular, individuals with severe psychosis (i.e., having poorer positive and negative syndrome scale [PANSS] and global assessment of functioning scale scores compared to less-severe psychosis) were at a higher risk of receiving antipsychotic medication that is not supported by treatment guidelines (Weinmann et al., 2005).

Millions of people use antipsychotic medications, including most of the 21 million people with schizophrenia (http://www.who.int/mediacentre/factsheets/fs396/en/). In Finland, as many as 4% of the population take antipsychotic medication. Thousands of clinicians (many of whom are nonpsychiatrists) prescribe and manage antipsychotic medications, which is a major global public health and

competency challenge when used these complicated medications. The proper use of antipsychotic medication—a key issue in clinical psychiatry—requires knowledge of evidence-based treatment approaches. There is an agreement that antipsychotics are efficacious during the acute and early maintenance phases of illness and up to 2–3 years after the acute episode (Correll, Rubio, & Kane, 2018; De Hert et al., 2015). Sustained antipsychotic treatment is associated with substantially decreased symptomatology, relapses, and mortality (Tiihonen, Tanskanen, & Taipale, 2018, Taipale et al., 2020). However, the pros and cons of long-term, including lifelong, treatment are less clear (Leucht, 2018).

Since the development of modern antipsychotic medications in the early 1950s, management practices have changed from authoritarian and paternalistic prescriptions by "doctor's order" into a more shared decision-making process that aims to minimize adverse effects and non-adherence. This collaborative attitude has its roots in moral treatment, civil rights, community psychiatry, and democratic values (Isohanni et al., 2018). This attitude also stresses collaborative and shared decision-making, patient-centered care, medication self-management, peer and family support, and personalized medicine. The therapeutic community movement (Isohanni 1983, 1993) supported shared decision-making and minimal use of antipsychotics. In the famous Soteria model, 43% of patients with schizophrenia (who were probably compliant and with overall mild illness severity) could be treated without antipsychotics (Bola & Mosher, 2003). In these models, medications were taken without coercion and adjusted to minimal dosages and durations (Bola et al., 2006).

Optimal antipsychotic treatment practices in the long-term management of schizophrenia have three main cornerstones (Isohanni et al., 2018): (1) evidence-based use of antipsychotics, (2) adjuvant psychosocial therapies, and (3) optimal medication management strategy. Multiple different models of medication management have been reported (Howard et al., 2009), but to the best of our knowledge, there are no reviews or universal recommendations on their content and efficacy.

Narrative reviews highlight new and unanswered topics that are difficult to analyze in systematic reviews and tend to focus on studies based on author selection (Uman et al., 2011). As far as we know, this is the first review on the topic. Our goal was that this seminal work would generate new research synthesis and clinical recommendations regarding this important topic. Our aim in this narrative review was, first of all, to analyze the existing literature on the definitions and models of medication management of antipsychotics in schizophrenia. Next, we focused on the effectiveness of medication management in controlled interventions with at least 2 years of follow-up. Finally, we present clinical recommendations for "real-world" antipsychotic medication management (Table 2).

2 | METHODS

We searched the relevant published literature on the medication management of antipsychotic treatment of schizophrenia. The literature search was carried out in May 2020 using the electronic databases of PubMed, Scopus, Web of Science, PsycARTICLES, and Cochrane and the following search terms: (medication management OR medication therapy management) AND schizophren* AND antipsychotic*. There were no restrictions regarding language, publication date, publication status, or study design, and the search was directed to standard search fields (Text Word in PubMed) except in PsycARTICLES, which was directed to All Text.

All identified studies were screened based on the title and abstract and defined as eligible/ineligible. The reference lists, including previous systematic reviews, were examined to identify all relevant studies. The articles were clustered to meet the following eligibility criteria: defining, measuring, and applying clinically medication management and its efficacy, especially in long-term (i.e., over 2 years) intervention studies in schizophrenia. We omitted discussion of antipsychotics in other psychiatric disorders outside of schizophrenia. There were no restrictions regarding language, publication date, publication status, or study design.

3 | RESULTS

3.1 | Search results

The search strategy identified potential relevant articles in PubMed ($n = 84$), Scopus ($n = 127$), Web of Science ($n = 48$), PsycARTICLES ($n = 108$), and Cochrane ($n = 42$). After removing duplicates, we reviewed 277 articles. Based on the search results, there is no unified approach for optimal medication management, but multiple useful strategies are presented for individual patients, prescribers, and organizations. Such diverse data are difficult to analyze in a systematic review. Therefore, a narrative review was constructed which highlights new and unanswered topics that focus on studies based on author selection (Uman et al., 2011).

3.2 | Defining, measuring, and clinically applying medication (therapy) management

3.2.1 | Definitions

As a MeSH term (introduced in 2008), medication therapy management is broadly defined as assistance in managing and monitoring drug therapy, consulting with patients and their families on the proper use of medication; conducting wellness and disease prevention programs to improve public health; overseeing medication use in a variety of settings. Medication therapy management is a distinct service that optimizes therapeutic outcomes for individual patients (APHa Foundation, 2020) regarding access, content, and practices of medication and also compliance and response. The phase of the illness (e.g., first-episode vs. chronic illness) and local and national treatment standards are taken into account.

The term "medication management" is not consistently defined in the literature and sometimes used as a synonym of medication therapy management, although usually it is more narrowly defined than medication therapy management and stresses clinical collaboration between patient and therapist/treatment team (e.g., Gray et al., 2004; Hansen et al., 2018; Howard et al., 2009). In this study, we use mainly the term "medication management" and stress patient–therapist interaction, but we also address guideline adherence and organizational aspects of medication (see Table 2).

Measures of medication management are few and either patient-focused or aimed at care providers or organizations. The Medication Management Ability Assessment test consists of a doctor–patient role-play in which the subject is required to repeat a daily regimen of medication (Depp et al., 2008; Patterson et al., 2002). In addition, virtual reality assessment of medication management skills was developed and tested in the Virtual Reality Apartment Medication Management Assessment (VRAMMA). The aim of VRAMMA is to assess the ability of patients with schizophrenia to manage a simulated medication regimen in a multi-room apartment (Kurtz et al., 2007).

3.2.2 | Clinical models

The Medication Management Approaches in Psychiatry is an evidence-based practice to guide the use of psychotropic medications in the treatment of schizophrenia (El-Mallakh et al., 2014). Some trials of medication management/alliance training packages have been developed and reviewed by Gray and colleagues (Gray et al., 2010; McCabe et al., 2012). Less structured principles are also presented, the most important being appropriate indications, drug selection, and dosing, as well as shared decision-making in prescription, follow-up, and monitoring during regular appointments by a clinician, case manager, and patient (Howard et al., 2009). Careful documentation of drug response, continuity, and coordination of care should be performed by a well-trained multidisciplinary team (McCabe et al., 2012, 2013).

3.3 | Effectiveness of medication management interventions

3.3.1 | Cross-sectional, naturalistic, and short-term (<2 years) studies

Few efficacy studies were identified in this category. Nurses who had received medication management training, including a manualized package, contributed to a significantly higher reduction in patients' overall psychopathology (PANSS total), attitudes toward antipsychotic medication as measured with drug attitude inventory-30, and compliance compared with treatment as usual at the end of the 6-month study period (Gray et al., 2010). Training community mental health professionals in medication management had a positive impact on clinical outcomes and service user involvement in treatment (Harris et al., 2009). An enhanced guideline implementation strategy had some limited positive effects, illustrating the challenges of changing clinical behavior (Owen et al., 2008). A patient-centered strategy to identify and overcome barriers to adherence can improve adherence to antipsychotic medications (Hudson et al., 2008).

3.3.2 | Longitudinal (over 2 years of follow-up or study period) controlled studies including medication management intervention

In Table 1, longitudinal intervention studies ($n = 8$) with duration of at least 2 years are presented in detail. We identified three main aims related to medication management intervention: medication quality (El-Mallakh et al., 2013; Howard et al., 2009; Maples et al., 2012), dose tapering (Bergstrom et al., 2018; Calton et al., 2008; Isohanni 1983, 1993; Lehtinen et al., 2000), and adherence (Pitschel-Walz et al., 2006; Morken, Grawe, & Widen, 2007). There were a number of positive outcomes, but findings were overall mixed. Some evidence exists that systematic medication management may improve the risk-benefit balance of antipsychotics by achieving the lowest effective dose, minimizing adverse effects, simplifying medication regimen, and improving adherence.

4 | DISCUSSION

4.1 | Principal findings

This review identified broad data from different study designs investigating antipsychotic medication management in schizophrenia. Currently, there are multiple models and clinical applications regarding medication management. Systematic medication management may improve the risk-benefit balance of antipsychotics by achieving minimizing adverse effects and effective dosage, and improving adherence (Pitschel-Walz et al., 2006).

4.2 | Improving the quality of care

Based on the studies in Table 1, there is some evidence that optimal medication management may improve the risk-benefit balance of antipsychotics and decrease side effects and the use of hospital and crisis or emergency services.

4.3 | Minimizing effective doses

The efficacy of long-term antipsychotic treatment, especially at high doses, has been questioned (Harrow et al., 2017; Leucht, 2018). Current evidence-based guidelines are not explicit (especially in mid- and long-term illness duration) regarding optimal doses, dose tapering, or low-dose maintenance. Guidelines make low doses

possible, but do not suggest how to go about tapering (e.g., at what point in the clinical course of illness, and over what time period).

Adverse effects—including neurologic and metabolic side effects—related to antipsychotics are frequent and sometimes severe. Effects on brain volume appear to be dose-dependent: High cumulative doses are related to brain alterations (Veijola et al., 2014; Huhtaniska et al., 2017a) and cognitive decline (Husa et al., 2014). In addition, a meta-analysis focusing on long-term antipsychotic use and brain volume changes found associations between higher antipsychotic exposure and brain volume decrease in the parietal lobe and an increase in basal ganglia (Huhtaniska et al., 2017b).

There is limited evidence regarding doses above the therapeutic range other than in exceptional circumstances (Smith, Leucht, & Davis, 2019), and a general harm reduction strategy is to use the lowest effective dose (Dudley, Liu, & De Haan, 2017; Wunderink et al., 2007, 2013; Zhou et al., 2018). Strategies for personalized antipsychotic dosing and dose tapering may benefit a subgroup of patients, but may also be associated with incrementally increased risk of relapse or excess mortality. There is also little knowledge of how individual differences in pharmacokinetics and pharmacodynamics may influence the optimal dosage, efficacy, and tolerance, as well as the incidence of adverse effects of antipsychotics.

When optimizing the benefit-risk ratio and balancing symptomatic, functional, and somatic outcomes, one goal could be to aim for the lower ranges of effective dosing. However, what do the principles "lowest effective dose" or "according to individual patient needs" mean in clinical practice? It is known that the first episode of psychosis generally requires lower dosages (McEvoy, Hogarty, & Steingard, 1991). Uchida and colleagues found no differences between lower antipsychotic dose (50%–100% of the defined daily dose, DDD) and standard dosing, concerning overall treatment failure or hospitalization (Uchida et al., 2011). A very low dose (<50% of the DDD) was associated with a greater risk of hospitalization and illness relapse. Risk reduction of excess mortality was also achieved by low (<0.5 DDD) or moderate doses (0.5–1.5 DDD; Torniainen et al., 2015). Zhou et al., (2018) demonstrated that a dose reduction of 50% in risperidone or olanzapine did not lead to more severe symptomatology but improved cognition and negative symptoms. The current literature does not support the safe reduction of guideline-concordant antipsychotic dosing by 50% or more in stabilized individuals receiving initially moderate- or high doses (Correll et al., 2018). In first-episode psychosis samples, discontinuation strategies may elevate the relapse risk compared with maintenance antipsychotics (Hui et al., 2018). However, targeted discontinuation strategies may decrease this difference (Thompson et al., 2018).

4.4 | Discontinuing antipsychotics

No guideline-concordant prescribing consensus exists on the optimal duration of antipsychotic medication treatment, but there is a tendency toward recommending indefinite treatment in stabilized patients (Correll et al., 2018; De Hert et al., 2015). In long-term follow-up studies, about 20% (Moilanen et al., 2013; Wunderink et al., 2007) or 30% (Wils et al., 2017) of patients achieved remission in the absence of antipsychotics. Note, however, that a favorable clinical course predicted antipsychotic non-use. Thus, patients with good outcomes may be overrepresented in discontinuation studies. However, paradoxically, patients responding well to medication may be particularly at risk of relapse (Gaebel et al., 2016). A total of 10 out of 11 guidelines do not recommend discontinuation of antipsychotics within 5 years (Takeuchi et al., 2012). A shift to a low antipsychotic dosage after the first episode has been proposed (Correll et al., 2018; McGorry, Alvarez-Jimenez, & Killackey, 2013); but others insist on prolonged (Tiihonen et al., 2018) or even life-long (Emsley, 2017) maintenance treatment for first-episode of psychosis.

4.5 | Possibilities to improve adherence

Medication nonadherence is defined as "a case in which a person's behavior in taking medication does not correspond with agreed recommendations from health personnel" (http://www.who.int/chp/knowledge/publications/adherence report/en). Antipsychotic nonadherence or partial adherence (Dufort & Zipursky, 2019) are important risk factors for relapse and poor medication response. Nonadherence can be failing to fill or refill a prescription, discontinuing medication before completing therapy, or taking more or less or other medication than prescribed. Antipsychotic nonadherence is often underestimated by the treatment team, and nondisclosure is common. Illness denial and comorbid substance use may be significant predictors of intentional nonadherence (Wilk et al., 2006, 2008).

Currently, there are no easy and accurate methods to assess adherence. Roughly half of patients with schizophrenia have some form of antipsychotic nonadherence (Barkhof et al., 2012; Dufort & Zipursky, 2019; Osterberg & Blaschke, 2005), which predicts risk of relapse and hospitalization, reduced effectiveness of subsequent treatment, waste of health care resources, increased substance use, poor quality of life, and increased suicide risk (Semahegn et al., 2018). Having multiple prescribers and co-management of medications may increase the risk of discontinuation in medication management (Hansen et al., 2018) and nonadherence (Farley et al., 2011). Paying attention to side-effects and adjusting to the lowest effective and tolerated dose could decrease nonadherence (Garcia et al., 2016).

Despite decades of focused research, a unified approach that significantly increases adherence rates has not been identified (Dufort & Zipursky, 2019). Identifying a patient's adherence trajectory may facilitate customization of interventions to improve adherence, including elements of medication management, namely simplifying medication regimens, using psychoeducation, engaging family support (J. E. Wilk et al., 2008), employing medication robots and other electronic interventions (Velligan et al., 2013), and even using holistic "adherence therapy" (Gray et al., 2004, 2010). Key existing recommendations for managing nonadherence stress the therapeutic relationship (McCabe et al., 2012, 2013) and patient and family inclusion (Correll et al., 2018; J. Wilk et al., 2006, J. E. Wilk et al., 2008).

TABLE 1 Controlled studies on content and results of medication management interventions in schizophrenia (total duration of the project over 2 years)

References	Number of patients, duration and main content of the project; follow-up time	Medication management intervention and regimen for medication management. The results of the intervention	Comments
Improving the quality of medication			
Howard et al., 2009 El-Mallakh et al., 2013	▪ Six mental health centres, 30 medical records in each, 14 prescribers ▪ Three years 1990–1994. Mirror-image design: 18-item scale to assess baseline versus posttraining prescriber fidelity at 4-month intervals over a period of 30 months. ▪ Prescriber education: designated trainers at baseline and annually focused on medication algorithms and symptom ratings in MedMAP ▪ Scoring of the prescriber fidelity scale required review of the medical records to identify documentation indicating adherence to MedMAP guidelines	▪ Evidence-based MedMAP was developed to guide the management of psychotropic medications for schizophrenia ▪ Training significantly improved prescriber adherence to some items of MedMAP ▪ Posttraining improvement was greatest in patient education, documentation of illness and medication history, and simplification of medication regimen ▪ Organizational support is essential for successful implementation of evidence-based practices in medication management	▪ The MedMAP project was the first longitudinal effort to implement a medication management program in a community mental health treatment setting. ▪ This medication management model includes 7 domains and 22 measurable items ▪ Old study, limited power, and amount of prescribers ▪ No RCT but mirror-image study ▪ Medication practices in health centres under study not described in detail
Maples et al., 2012	▪ Three hundred and twenty five patients (schizophrenia spectrum and bipolar disorders) and 345 patients in comparison group ▪ Two years (12 months before enrolment, 6-month intervention, 6-month follow-up)	▪ Medication management coordinators aimed at enhanced continuity during transition from inpatient to outpatient care, informed the treating psychiatrists, provided medication education, and guideline-concordant prescribing ▪ Medication management program improved continuity of care and decreased use of hospital, crisis, or emergency services. ▪ Additional interventions may be required to address crisis care and reduce rehospitalizations	▪ No detailed diagnostic data on two patient groups ▪ Focus mainly on continuity of care ▪ Potential residual confounding by diagnosis, site and indication ▪ No measures of adherence
Dose tapering studies			
Calton et al., 2008	▪ Three controlled trials with 223 participants diagnosed with first- or second-episode schizophrenia between 1970 and 90s ▪ The "Soteria paradigm" using a minimal medication approach. 2-year follow-up	▪ Antipsychotic medications taken based on choice and without coercion, dosages were adjusted to the lowest dose and shortest duration based on self-observation and staff report ▪ Soteria model without the use of antipsychotic medication as the primary treatment seemed to be as effective as traditional hospital-based treatment. ▪ However, few significant differences between the experimental and control groups in any of the trials across a range of outcome measures, though some benefits in specific areas	▪ ICD schizophrenia with benign course: probable selection and attrition biases ▪ No standardized data on antipsychotic definition, measurement and use are presented ▪ Costs, harms, and side effect burden in both models were not estimated

(Continues)

TABLE 1 (Continued)

References	Number of patients, duration and main content of the project; follow-up time	Medication management intervention and regimen for medication management. The results of the intervention	Comments
Isohanni, 1983 Isohanni, 1993	▪ Annual neuroleptic doses of developing TC ward for acute psychoses (20 patients/year) were calculated and compared (1979) to 5 traditional psychosis wards ▪ Duration of the TC developmental project with mirror-image design between 1965 and 1982: ward under study was a traditional closed ward in 1965–1970 and TC ward in 1971-1982	▪ Medication management done by a multidisciplinary team. Patient and family education on drugs and participation in decisions. Main aims: lowest effective dose and clinical remission. ▪ TC model with medication management reduced the mean dose of antipsychotics in TC ward from 370 mg/day chlorpromazine equivalents (1965) to 160 mg/day (1982). In 1979, the costs of medication were 25%–50% of the costs in traditional psychosis wards. 8% of patients in TC had extrapyramidal symptoms contrasted to 15%–21% in traditional psychosis wards	▪ Symptom control and remission were achieved in TC ward using low doses of antipsychotics when pooled with psychosocial and psychoeducational activities ▪ No follow-up of symptoms or other outcomes in posthospital care ▪ Old study (1965–1982), long study period ▪ TC model with long stay (1–2 months) possible during study period, but not presently
Lehtinen et al., 2000	▪ Experimental (67 functional non-affective psychoses) and control (39) groups in 1992–1993. Both groups were treated according to the 'need-specific Finnish model' stressing teamwork, patient and family participation, and psychotherapeutic attitudes ▪ Follow-up 2 years after the basic survey	▪ Antipsychotic use was minimal in the experimental group. The control group treated according to the usual Finnish practice (favoring in 1990s their routine use at the smallest effective doses) ▪ In the experimental group 42.9% did not receive neuroleptics versus 5.9%. in the control group. Outcomes (time in hospital, psychotic symptoms, employment, GAF) of the experimental group was equal or better than in control group after controlling for age, gender and diagnosis	▪ Many of the patients with first-episode psychosis were treated without neuroleptics ▪ Integrated intensive psychosocial approach may reduce the need of antipsychotics ▪ One third of patients had non-schizophrenic psychosis ▪ No subgroup or cost-effective analyses ▪ No data on drug selection or dosing ▪ Old study and data (1992–1993)
Bergström et al., 2018	▪ One hundred and eight first-episode non-affective psychosis cases in OD model, 1783 controls from registers having TAU. ▪ Median follow-up 19-20 years, study years from mid-1990s–early 2000s	▪ OD approach is a family-oriented early intervention stressing immediate and flexible help, dialogue within social network, selective, and minimal use of antipsychotics ▪ Need for neuroleptics was significantly lower in OD model during the follow-up: one third to half used neuroleptics in OD but nearly all in TAU. ▪ In OD model, durations of hospital treatment, disability allowances were more favorable contrasted to TAU. During follow-up, no differences were found in annual incidence of FEP, diagnosis, and suicide	▪ Long follow-up ▪ Detailed description of clinically innovative intervention (OD) but not TAU ▪ Recent study, multiple use of excellent Finnish registers ▪ No subgroup (diagnosis, medication) analyses ▪ Only superficial register data on antipsychotics: no detailed medication doses, indications or trajectories ▪ Potential confounding by diagnosis, individual treatments, site, long follow-up period (19–20 years) and indication
Adherence studies			
Pitschel-Walz et al., 2006	▪ Two hundred and 36 inpatients were randomly assigned to intervention or routine care. ▪ 2 years follow-up 1990–1994 ▪ Intervention was eight psychoeducational sessions to patients and their families over a period of 4–5 months	▪ In the intervention group compliance was increased after 12 (good compliance in 80% vs. 58%) and 24 months (good compliance 80% vs. 55%) ▪ Rehospitalizations reduced in 12-month follow up (21% vs. 32%) and 24-month follow-up (41% vs. 58%)	▪ The authors concluded: psychoeducation should be routinely offered to all schizophrenia individuals and their families. ▪ Routine care (TAU) not described in detail ▪ Old study

TABLE 1 (Continued)

References	Number of patients, duration and main content of the project; follow-up time	Medication management intervention and regimen for medication management. The results of the intervention	Comments
Morken et al., 2007	▪ Integrated versus standard treatment for 50 patients between 1992 and 1999 ▪ Two years follow-up of adherence	▪ In integrated arm: assertive community treatment, family psychoeducation and involvement, and social skills training ▪ No effects of integrated treatment on medication adherence were found	▪ Limited power, standard treatment not in detail described

Abbreviations: FEP, first-episode of psychosis; GAF, global assessment of functioning scale; MedMAP, Medication Management Approaches in Psychiatry; OD, open dialogue; RCT, randomized controlled trials; TAU, treatment as usual; TC, therapeutic community.

Long-acting injectable antipsychotics (LAIs) may decrease compliance problems and improve effectiveness (Kishimoto et al., 2018) but presuppose team training and patient education (Kane et al., 2019). Although LAIs are used widely especially in patients with a high risk of treatment resistance, nonadherence and relapse, robust and unambiguous evidence of their superior efficacy compared to oral antipsychotics is difficult to be proven. This is based primarily on methodological reasons, because in a respective randomized controlled trials (RCT), the treatment with oral antipsychotics is associated with a higher adherence due to the study situation than normally. Due to the insecure evidence, guideline recommendations are rather cautious.

4.6 | Clinical implementation of medication management

Findings indicate that facilitators of medication management include practitioner recognition of their value, consumer involvement, collaboration, continuity of care, and fidelity assessments. Barriers to their implementation are problematic technology, workflow issues, lack of flexibility in prescribers' ability to implement guidelines, regulatory and financial barriers, consumer insurance status (El-Mallakh et al., 2014), and cognitive limitations decreasing medication management skills (Depp et al., 2008; Kurtz et al., 2007; Lam et al., 2013; Raskin et al., 2014).

Three perspectives or levels of antipsychotic medication therapy management appeared in the reviewed literature: (1) patient perspectives, (2) prescriber or therapist or team perspectives, and (3) organizational perspectives. These perspectives are considered in Table 2, where our recommendations based on relevant literature and author opinions are summarized.

We propose that in clinical practice, the administrators, prescribers, and teams prescribing antipsychotics discuss how these principles are adapted in their everyday clinical work. Most schizophrenia treatment algorithms are inconsistent and unsound due to a lack of evidence (Gaebel, Riesbeck, & Wobrock, 2011), which stresses individualized medication management. A 1–3 month test period with careful medication management may be useful when antipsychotics are switched (e.g., to clozapine), tapered or stopped, and when the response to medication is difficult to predict.

The study sample has a significant influence on the results and clinical recommendations. For instance, first-episode psychosis is a heterogeneous population. Some of these subjects may have non-schizophrenic psychosis, which may require only short-term antipsychotic medication. One part of proper medication management is longitudinal diagnostic follow-up.

Schizophrenia is usually a life-long disease. The clinical reality is that prescribers and treatment teams tend to change. Ending treatment relationships and starting new ones pose risks (Isohanni, 1983).

Antipsychotics diminish illness expression by altering brain chemistry, alleviating acute illness episodes and preventing relapses. Medication management influences how antipsychotics restore adversely affected brain functions. Antipsychotics are powerful tools: their effect sizes are similar to the treatment of chronic conditions in other fields of medicine (Leucht et al., 2012). Adverse effects and low adherence rates are common, especially during absent or poor medication management (Breadon & Kulkarni, 2019). Somatic harms are common, although antipsychotics do not necessarily increase severe physical comorbidity (Taipale et al., 2020). Positive outcomes and recovery in schizophrenia are still suboptimal (Jääskeläinen et al., 2013), which may be partly attributable to poor medication management.

5 | UNANSWERED QUESTIONS AND DIRECTIONS FOR FUTURE RESEARCH

This narrative review revealed some understudied topics related to medication management. There were a small number of recent studies, and the majority of studies were performed at illness onset or during short (<2 years) follow-up periods, although most patients are ill for more extended periods or are in midlife or older. RCT in longitudinal studies are difficult to conduct and tend to be reductionistic when analyzing the complex, even life-span interactions between brain, environment, and drug effects (Isohanni et al., in press), also the effects of medication management. Observational, naturalistic, nonexperimental study settings are realistic when investigating the complex long-term effects of antipsychotics. However, the patients are not treated randomly, which may cause residual confounding (e.g., by indication). Very sick patients often get longer treatments and higher doses of antipsychotics. Patients with frequent relapses also tend to receive more medications and higher

TABLE 2 Key perspectives and clinical practices in medication therapy management approaches of antipsychotics, especially in long term care

Patient perspectives	• Documenting illness and medication histories, clinical responses and efficacies, side effects, and adherence trajectories • Addressing patients' experiences, beliefs about antipsychotics, and medication self-management skills • Patient and family inclusion in planning, decisions and adherence strategies • Organizing optimal medication management visit frequency and content • When antipsychotics are started, switched (e.g., to clozapine or long-acting injectable antipsychotics), tapered or stopped, a 1–3 months experimental period with well-planned medication management is often useful
Prescriber and treatment team perspectives	• Orientation to guidelines (e.g. NICE or PORT 2009), reviews and meta-analyses aiming at appropriate medication choice, dose, and cost-effectiveness • Considering diagnostic follow-up, symptom trajectories, remission, recovery, cognitive capacities, somatic illness, aging, adjunctive medications, disclosing of nonadherence, and detection of treatment-refractory patients • Minimizing errors in medication decisions, with rapid correction and diagnosis • Team work and shared decision making must be applied especially in critical situations: early warning signs, relapse, antipsychotic-resistance, nonadherence, negative drug attitudes, women in pregnancy, multiple prescribers, staff turnover, changes in treatment
Organizational perspectives	• Unified clinical models for optimal medication management visits and practices do not exist but there are multiple useful practices • It may be challenging to change clinical medication practices • Coordinated care within a good organizational climate rests on a participatory relationship, shared decision-making and moderate medication consensus between patients, relatives, frontline clinicians, the treatment team, and the administration
In summary	• Personalized, tailored medication management is needed especially in midlife and in elderly patients with schizophrenia when guideline-concordant algorithms are vague • Medication management may range from simple to extensive • The combination of antipsychotics, psychoeducation and psychosocial interventions under the umbrella of proper medication management should be routinely offered to all patients with schizophrenia

doses, while patients with less severe symptoms receive lower doses or trials without antipsychotics.

Specific antipsychotic-related problems among older patients with schizophrenia are minimally studied. As in several other mental and cognitive disorders, aging of the brain is greater in schizophrenia than in healthy subjects (Kaufmann et al., 2019). However, age-related changes in pharmacokinetics and pharmacodynamics, and in the blood-brain barrier, have minimally been studied in relation to antipsychotic use in schizophrenia. All of these factors have effects on optimal dosing as well as on the risks of adverse effects (Citrome, 2017). Antipsychotics increase the risk of falls and fractures and negative cardiovascular outcomes, especially among persons with preexisting cardiovascular disease (J. Seppala et al., 2019). The risk-benefit balance for antipsychotics demands a comprehensive assessment and individual treatment to make proper choices of specific medications, doses, and to consider drug–drug and drug-disease interactions, especially in the case of somatic comorbidities. Somatic comorbidities increase the number of prescribers and medications, and this fragmentation increases the challenges of proper medication management (Farley et al., 2017).

The combination of antipsychotics and psychosocial therapies is part of most treatment recommendations but is also minimally studied. One reason may be the diversity of available psychosocial therapies. Compared with usual care alone, psychosocial interventions improve functional outcomes, quality of life, core illness symptoms, and reduce relapses in schizophrenia (Cooper et al., 2019). In combined therapy, one major aim is to strengthen medication compliance by increasing the understanding of the meanings and aims of antipsychotics (Kay, 2007).

5.1 | Economic evaluation and healthcare resource utilization

Extensive medication management (as proposed in Table 2) probably increases immediate costs. We did not find studies examining whether possible positive outcomes (rational, smallest effective doses of medication, reduction of relapses, and rehospitalizations) would reduce total costs.

General public views on antipsychotics, including their pros and cons, are minimally studied, even though disagreements and conflicts around antipsychotics between professionals and some laymen groups are still prevalent. An accusation and demonizing attitude against antipsychotics are common in lay websites and demonstrations. The experiences with and status of antipsychotics may be different from lay, Internet, and other media populations in contrast

to prescribers (Adibi, 2015; Gray et al., 2004). It is not known whether proper medication management influences these conflicting attitudes.

Ethical and legal issues provide guidance for medication management, especially Hippocrates' principle: primum non nocere (first, do no harm). Alternatively: minimize or avoid the iatrogenic global burden of antipsychotics, including harmful adverse effects. The risk of long-term harm is one reason to consider minimizing antipsychotic doses by maximizing psychosocial treatments and medication management. According to the Finnish legislation on patient rights, the patient must accept their treatments.

5.2 | Prescribers' attitudes and biases

The longer the duration of illness, the less clear is associated medication algorithms and recommendations. This situation may increase the effect of the prescriber's attitudes and unrecognized biases. Proper training, supervision, teamwork, and consultations could decrease these potential harmful influences (Kay, 2007). Experienced clinicians often treat complicated, relapsed, treatment-resistant patients and find limited success, while cases with good response and recovery are often lost to follow-up ("the clinician's illusion"). This "pessimism bias" or sampling bias may reduce clinicians' confidence to taper, change, or discontinue antipsychotics (Isohanni et al., in press). Scientists in academic and research environments may be distanced from clinical reality and experience "ivory tower bias," which may lead to non-evidence-based treatment, for example, under- or over-estimation of the effect of antipsychotics or consideration of interindividual variation of their efficacy.

5.3 | Modern technology

A future challenge is to increase mHealth (i.e., mobile health) applications or electronic health and mobile devices (Donker et al., 2013), mainly wearable devices like mobile phones, to provide objective long-term data to monitor medication effects, compliance, symptoms, or treatment progress. Information may range from skin conductance and temperature to a number of exchanged short message service text messages to a number of incoming and outgoing calls and electronic reminders. The variety of easily acquirable personal data offers a unique opportunity to study lifestyle and behavior at the physical, cognitive, and environmental level (Kreyenbuhl et al., 2019; J. Seppala et al., 2019; Torous et al., 2018). These data may initiate a new trend in health care provision characterized by more personalized interventions.

6 | CONCLUSIONS

Howard et al. (2009) previously defined medication management. Based on this literature review, we have slightly reformulated this definition:

Medication management is an ongoing process to organize and monitor the recommended use of antipsychotics, aiming at the facilitation of their cost-effective, adherent, and acceptable use. Medication management is implemented in an optimal organizational environment, teamwork, and therapeutic alliance.

There are no anticipated breakthroughs in antipsychotic medication efficacy. In this stagnated situation, optimal medication management is a realistic goal to improve the risk-benefit ratio of antipsychotics. This review suggests possibilities for how to tease out greater efficacy of antipsychotics using sophisticated and active medication management. The longer the duration of schizophrenia, the less distinct is antipsychotic treatment algorithms and recommendations, and the more individualized treatment decisions and proper medication management are needed. Additional, well-designed naturalistic studies and clinical trials are needed to determine the content and long-term efficacy of medication management in schizophrenia.

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CONFLICT OF INTEREST

Author Jari Tiihonen has had research collaboration with Eli Lilly and Janssen-Cilag, lecture fees from Eli Lilly, Janssen-Cilag, Lundbeck, and Otsuka. Author Sirpa Hartikainen: lecture fee from Astellas.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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