Medication management of antipsychotic treatment in schizophrenia – a narrative review

Matti Isohanni[1] M.D., Ph.D., Erika Jääskeläinen[1] M.D., Ph.D., Brian J. Miller[2] M.D., Ph.D., M.P.H., Anja Hulkko[1] M.D., Ph.D.,[1], Jari Tiihonen[3,4] M.D., Ph.D., Hans-Jurgen Möller[5] M.D., Ph.D., Sirpa Hartikainen[6] M.D., Ph.D., Sanna Huhtaniska[1] M.D., Ph.D., Johannes Lieslehto[1] M.D., Ph.D.

1 Center for Life Course Health Research, University of Oulu, Finland.
2 Department of Psychiatry, Augusta University, 997 St. Sebastian Way Augusta, GA 30912.
3 Karolinska Institutet, Department of Clinical Neuroscience, Stockholm, Sweden
4 University of Eastern Finland, Department of Forensic Psychiatry, Kuopio, Finland.
5 Department of Psychiatry, Ludwig-Maximilians-University, Munich, Germany.
6 Kuopio Research Center of Geriatric care, School of Pharmacy, University of Eastern Finland, Kuopio, Finland.

Corresponding author: Johannes Lieslehto, M.D., Ph.D., johannes.lieslehto@oulu.fi, Center for Life Course Health Research, University of Oulu, Finland.

Short title: Medication management of antipsychotics

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** two 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

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

Word count

Main text: 4113, Abstract: 165

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 PANSS and GAF scores compared to less-severe psychosis) were** at a higher risk of receiving antipsychotic medication that is not supported by treatment guidelines (Weinmann, Janssen and Gaebel, 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 non-psychiatrists) 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 **two to three** years after the acute episode (De Hert *et al.*, 2015; Correll, Rubio and Kane, 2018). Sustained antipsychotic treatment is associated with substantially decreased symptomatology, relapses, and mortality (**Tiihonen et al., 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; Isohanni 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 and 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 two 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-year) 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

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, Howard et al., 2009, Hansen et al., 2018). In this paper 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 (MMAA) test consists of a doctor-patient role-play in which the subject is required to repeat a daily regimen of medication (Patterson *et al.*, 2002; Depp *et al.*, 2008). 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).

Clinical models. The Medication Management Approaches in Psychiatry (MedMAP) 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 towards antipsychotic medication (DAI–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 two 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** two years are presented in detail. We identified three main aims related to medication management intervention: medication quality (Howard *et al.*, 2009; Maples *et al.*, 2012; El-Mallakh *et al.*, 2013), dose tapering (Isohanni 1983; Isohanni 1993; Lehtinen *et al.*, 2000; Calton *et al.*, 2008; Bergstrom *et al.*, 2018), and adherence (Pitschel-Walz *et al.*, 2006; Morken, Grawe and 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.**

[Insert Table 1 approximately here]

4. Discussion

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 improv**ing** adherence (Pitschel-Walz *et al.*, 2006).

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.

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, Jaaskelainen, Heikka, *et al.*, 2017) 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, Jaaskelainen, Hirvonen, *et al.*, 2017).

There is **limited** evidence regarding doses above the therapeutic range other than in exceptional circumstances (Smith, Leucht and Davis, 2019), and a general harm reduction strategy is to **use the** lowest effective **dose** (Wunderink *et al* 2007, 2013; Dudley, Liu and De Haan, 2017; 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 and 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, Rubio and Kane, 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).

Discontinuing antipsychotics. No guideline-concordant prescribing consensus exists on the optimal duration of antipsychotic medication treatment, but there is a tendency towards recommending **indefinite** treatment in stabilized patients (De Hert *et al.*, 2015; Correll, Rubio and Kane, 2018). In

long-**term** follow-up studies, about 20% (Wunderink *et al.*, 2007; Moilanen *et al.*, 2013) 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 five years (Takeuchi *et al.*, 2012). A shift to a low **antipsychotic** dosage after the first episode **has been proposed** (McGorry, Alvarez-Jimenez and Killackey, 2013; Correll, Rubio and Kane, 2018); **but** others insist on prolonged (Tiihonen, Tanskanen and Taipale, 2018) or even life-long (Emsley, 2017) **maintenance treatment for FEP**.

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 and 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 (Osterberg and Blaschke, 2005; Barkhof *et al.*, 2012; Dufort and Zipursky, 2019), 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 non-adherence (Garcia *et al.*, 2016).

Despite decades of focused research, a unified approach that significantly increases adherence rates has not been identified (Dufort and 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 (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 non-adherence stress **the** therapeutic relationship (McCabe *et al.*, 2012, 2013) and patient and family inclusion (Wilk *et al.*, 2006, 2008; Correll, Rubio and Kane, 2018).

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, non-adherence 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 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.

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 (Kurtz *et al.*, 2007; Depp *et al.*, 2008; 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.

[Insert Table 2 approximately here]

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 and Wobrock, 2011), which stresses individualized medication management. A **one to three** 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 and 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 **under**studied 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. Randomized controlled trials (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, non-experimental 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 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 **pre-**existing cardiovascular disease (L. 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).

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 (Gray *et al.*, 2004; Adibi 2015). 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.

Prescribers' attitudes and biases. The longer the duration of illness, the less clear are 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 2016). 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,** e.g., under- or over-estimation of the effect of antipsychotics or **consideration of** interindividual variation of their efficacy.

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 (SMS) 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 (Torous *et al.*, 2018; J. Seppala *et al.*, 2019; Kreyenbuhl *et al.*, 2019). 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 are 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.

Financial support: This study was supported financially by the Finnish Medical Association (JL), Yrjö Jahnsson Foundation (J.L.), and Jalmari and Rauha Ahokas Foundation (J.L.).

Conflict of interest during the last three years: 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.

References

Adibi S. Introduction. In: Adibi S, editor. Mobile Health: A Technology Road Map. Cham, Switzerland: *Springer International Publishing*; 2015, p 1-10.

APHa Foundation. https://aphafoundation.org/medication-therapy-management. Enhanced on May 10 2020.

Barkhof, E. *et al.* (2012) 'Interventions to improve adherence to antipsychotic medication in patients with schizophrenia--a review of the past decade.', *European psychiatry : the journal of the Association of European Psychiatrists*, 27(1), pp. 9–18. doi: 10.1016/j.eurpsy.2011.02.005.

Bergstrom, T. *et al.* (2018) 'The family-oriented open dialogue approach in the treatment of first-episode psychosis: Nineteen-year outcomes.', *Psychiatry research*, 270, pp. 168–175. doi: 10.1016/j.psychres.2018.09.039.

Bola, J. R. *et al.* (2006) 'Predicting medication-free treatment response in acute psychosis: cross-validation from the Finnish Need-Adapted Project.', *The Journal of nervous and mental disease*, 194(10), pp. 732–739. doi: 10.1097/01.nmd.0000243080.90255.88.

Bola, J. R. and Mosher, L. R. (2003) 'Treatment of acute psychosis without neuroleptics: two-year outcomes from the Soteria project.', *The Journal of nervous and mental disease*, 191(4), pp. 219–229. doi: 10.1097/01.NMD.0000061148.84257.F9.

Breadon, C. and Kulkarni, J. (2019) 'An update on medication management of women with schizophrenia in pregnancy.', *Expert opinion on pharmacotherapy*, 20(11), pp. 1365–1376. doi: 10.1080/14656566.2019.1612876.

Calton, T. *et al.* (2008) 'A systematic review of the Soteria paradigm for the treatment of people diagnosed with schizophrenia.', *Schizophrenia bulletin*, 34(1), pp. 181–192. doi: 10.1093/schbul/sbm047.

Citrome, L. (2017) 'Activating and Sedating Adverse Effects of Second-Generation Antipsychotics in the Treatment of Schizophrenia and Major Depressive Disorder: Absolute Risk Increase and Number Needed to Harm.', *Journal of clinical psychopharmacology*, 37(2), pp. 138–147. doi: 10.1097/JCP.0000000000000665.

Cooper, R. E. *et al.* (2019) 'Psychosocial interventions for people with schizophrenia or psychosis on minimal or no antipsychotic medication: A systematic review.', *Schizophrenia research*. doi: 10.1016/j.schres.2019.05.020.

Correll, C. U., Rubio, J. M. and Kane, J. M. (2018) 'What is the risk-benefit ratio of long-term antipsychotic treatment in people with schizophrenia?', *World psychiatry : official journal of the World Psychiatric Association (WPA)*, 17(2), pp. 149–160. doi: 10.1002/wps.20516.

De Hert, M. *et al.* (2015) 'The Use of Continuous Treatment Versus Placebo or Intermittent Treatment Strategies in Stabilized Patients with Schizophrenia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials with First- and Second-Generation Antipsychotics.', *CNS drugs*, 29(8), pp. 637–658. doi: 10.1007/s40263-015-0269-4.

Depp, C. A. *et al.* (2008) 'Assessment of medication management ability in middle-aged and older adults with bipolar disorder.', *Journal of clinical psychopharmacology*, 28(2), pp. 225–229. doi: 10.1097/JCP.0b013e318166dfed.

Donker, T. *et al.* (2013) 'Smartphones for smarter delivery of mental health programs: a systematic review.', *Journal of medical Internet research*, 15(11), p. e247. doi: 10.2196/jmir.2791.

Dudley, K., Liu, X. and De Haan, S. (2017) 'Chlorpromazine dose for people with schizophrenia.', *The Cochrane database of systematic reviews*, 4, p. CD007778. doi: 10.1002/14651858.CD007778.pub2.

Dufort, A. and Zipursky, R. B. (2019) 'Understanding and Managing Treatment Adherence in Schizophrenia.', *Clinical schizophrenia & related psychoses*. doi: 10.3371/CSRP.ADRZ.121218.

El-Mallakh, P. *et al.* (2013) 'Organizational fidelity to a medication management evidence-based practice in the treatment of schizophrenia', *Journal of psychosocial nursing and mental health services*, 51(11), pp. 35–44. doi: 10.3928/02793695-20130809-01.

El-Mallakh, P. *et al.* (2014) 'Challenges of implementing a medication management evidence-based practice in a community mental health setting: results of a qualitative study.', *Issues in mental health nursing*, 35(7), pp. 517–525. doi: 10.3109/01612840.2014.888601.

Emsley, R. (2017) 'On discontinuing treatment in schizophrenia: a clinical conundrum', *npj Schizophrenia*, 3(1), p. 4. doi: 10.1038/s41537-016-0004-2.

Farley, J. F. *et al.* (2011) 'Continuity of antipsychotic medication management for Medicaid patients with schizophrenia.', *Psychiatric services (Washington, D.C.)*, 62(7), pp. 747–752. doi: 10.1176/ps.62.7.pss6207_0747.

Farley, J. F. *et al.* (2017) 'Continuity of medication management in Medicaid patients with chronic comorbid conditions: An examination by mental health status.', *General hospital psychiatry*, 45, pp. 25–31. doi: 10.1016/j.genhosppsych.2016.12.001.

Gaebel, W. *et al.* (2016) 'Predictors for symptom re-exacerbation after targeted stepwise drug discontinuation in first-episode schizophrenia: Results of the first-episode study within the German research network on schizophrenia.', *Schizophrenia research*, 170(1), pp. 168–176. doi: 10.1016/j.schres.2015.10.024.

Gaebel, W., Riesbeck, M. and Wobrock, T. (2011) 'Schizophrenia guidelines across the world: a selective review and comparison.', *International review of psychiatry (Abingdon, England)*, 23(4), pp. 379–387. doi: 10.3109/09540261.2011.606801.

Garcia, S. *et al.* (2016) 'Adherence to Antipsychotic Medication in Bipolar Disorder and Schizophrenic Patients: A Systematic Review.', *Journal of clinical psychopharmacology*, 36(4), pp. 355–371. doi: 10.1097/JCP.0000000000000523.

Gray, R. *et al.* (2004) 'Effect of a medication management training package for nurses on clinical outcomes for patients with schizophrenia: cluster randomised controlled trial.', *The British journal of psychiatry : the journal of mental science*, 185, pp. 157–162. doi: 10.1192/bjp.185.2.157.

Gray, R. *et al.* (2010) 'Enhancing medication adherence in people with schizophrenia: an international programme of research.', *International journal of mental health nursing*, 19(1), pp. 36–44. doi: 10.1111/j.1447-0349.2009.00649.x.

Hansen, R. A. *et al.* (2018) 'Continuity of Medication Management among Adults with Schizophrenia and Comorbid Cardiometabolic Conditions', *Journal of pharmaceutical health services research: an official journal of the Royal Pharmaceutical Society of Great Britain*, 9(1), pp. 13–20. doi: 10.1111/jphs.12201.

Harris, N. *et al.* (2009) 'An evaluation of a medication management training programme for community mental health professionals; service user level outcomes: a cluster randomised controlled trial.', *International journal of nursing studies*, 46(5), pp. 645–652. doi: 10.1016/j.ijnurstu.2008.10.010.

Harrow, M. *et al.* (2017) 'A 20-Year multi-followup longitudinal study assessing whether antipsychotic medications contribute to work functioning in schizophrenia.', *Psychiatry research*, 256, pp. 267–274. doi: 10.1016/j.psychres.2017.06.069.

Howard, P. B. *et al.* (2009) 'Prescriber fidelity to a medication management evidence-based practice in the treatment of schizophrenia.', *Psychiatric services (Washington, D.C.)*, 60(7), pp. 929–935. doi: 10.1176/ps.2009.60.7.929.

Hudson, T. J. *et al.* (2008) 'Guideline implementation and patient-tailoring strategies to improve medication adherence for schizophrenia.', *The Journal of clinical psychiatry*, 69(1), pp. 74–80. doi: 10.4088/jcp.v69n0110.

Huhtaniska, S., Jaaskelainen, E., Heikka, T., *et al.* (2017) 'Long-term antipsychotic and benzodiazepine use and brain volume changes in schizophrenia: The Northern Finland Birth Cohort 1966 study.', *Psychiatry research. Neuroimaging*, 266, pp. 73–82. doi: 10.1016/j.pscychresns.2017.05.009.

Huhtaniska, S., Jaaskelainen, E., Hirvonen, N., *et al.* (2017) 'Long-term antipsychotic use and brain changes in schizophrenia - a systematic review and meta-analysis.', *Human psychopharmacology*, 32(2). doi: 10.1002/hup.2574.

Hui, C. L. M. *et al.* (2018) 'Long-term effects of discontinuation from antipsychotic maintenance following first-episode schizophrenia and related disorders: a 10 year follow-up of a randomised, double-blind trial.', *The lancet. Psychiatry*, 5(5), pp. 432–442. doi: 10.1016/S2215-0366(18)30090-7.

Husa, A. P. *et al.* (2014) 'Lifetime use of antipsychotic medication and its relation to change of verbal learning and memory in midlife schizophrenia - An observational 9-year follow-up study.', *Schizophrenia research*, 158(1–3), pp. 134–141. doi: 10.1016/j.schres.2014.06.035.

Isohanni M. The psychiatric ward as a therapeutic community. Doctoral dissertation. Acta Universitatis Ouluensis 1983; D 111: 5.

Isohanni, M.: The therapeutic community movement in Finland: past, current and future trends. Therapeutic Communities 1993;14:81-90

Isohanni, M. *et al.* (2018) 'Under-utilized opportunities to optimize medication management in long-term treatment of schizophrenia.', *World psychiatry : official journal of the World Psychiatric Association (WPA)*, 17(2), pp. 172–173. doi: 10.1002/wps.20523.

Isohanni, M. *et al.* (in press) Life span development of schizophrenia: symptoms, clinical course and outcomes. In: Tamminga CA, Ivleva EI, Reininghaus U, Van Os J. editors.Dimensions of Psychosis: Comprehensive Conceptualization and Treatments. New York, NY: Oxford University Press.

Jaaskelainen, E. *et al.* (2013) 'A systematic review and meta-analysis of recovery in schizophrenia.', *Schizophrenia bulletin*, 39(6), pp. 1296–1306. doi: 10.1093/schbul/sbs130.

Kane, JM. *et al.* (2019) *J Clin Psychiatry.* Apr 23;80(3):18m12546. doi: 10.4088/JCP.18m12546.

Kaufmann, T. *et al.* (2019) 'Common brain disorders are associated with heritable patterns of apparent aging of the brain.', *Nature neuroscience*, 22(10), pp. 1617–1623. doi: 10.1038/s41593-019-0471-7.

Kay J. Psychotherapy and medication. In: Gabbard GO, Beck JS, Holmes J editors. Oxford Textbook of Psychotherapy. Oxford University Press, USA 2007 p. 463-475.

https://www.ncbi.nlm.nih.gov/pubmed/?term=Kishimoto%20T%5BAuthor%5D&cauthor=true&cauthor_uid=29868849

Hagi, K. *et al.* (2018) 'Effectiveness of long-acting injectable vs oral antipsychotics in patients with schizophrenia: a meta-analysis of prospective and retrospective cohort studies.' Schizophrenia Bulletin; 44:603-619. doi: 10.1093/schbul/sbx090.

Kreyenbuhl, J. *et al.* (2019) 'Development and Feasibility Testing of a Smartphone Intervention to Improve Adherence to Antipsychotic Medications.', *Clinical schizophrenia & related psychoses*, 12(4), pp. 152–167. doi: 10.3371/CSRP.KRRE.070816.

Kurtz, M. M. *et al.* (2007) 'A virtual reality apartment as a measure of medication management skills in patients with schizophrenia: a pilot study.', *Schizophrenia bulletin*, 33(5), pp. 1162–1170. doi: 10.1093/schbul/sbl039.

Lam, J. W. S. *et al.* (2013) 'Prospective memory predicts medication management ability and correlates with non-adherence to medications in individuals with clinically stable schizophrenia.', *Schizophrenia research*, 147(2–3), pp. 293–300. doi: 10.1016/j.schres.2013.04.010.

Lehtinen, V. *et al.* (2000) 'Two-year outcome in first-episode psychosis treated according to an integrated model. Is immediate neuroleptisation always needed?', *European psychiatry : the journal of the Association of European Psychiatrists*, 15(5), pp. 312–320. doi: 10.1016/s0924-9338(00)00400-4.

Leucht, S. *et al.* (2012) 'Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses.', *The British journal of psychiatry : the journal of mental science*, 200(2), pp. 97–106. doi: 10.1192/bjp.bp.111.096594.

Leucht, S. (2018) 'Is there compelling evidence that schizophrenia long-term treatment guidelines should be changed?', *World psychiatry : official journal of the World Psychiatric Association (WPA)*, 17(2), pp. 166–167. doi: 10.1002/wps.20520.

Maples, N. J. *et al.* (2012) 'Can medication management coordinators help improve continuity of care after psychiatric hospitalization?', *Psychiatric services (Washington, D.C.)*, 63(6), pp. 554–560. doi: 10.1176/appi.ps.201100264.

McCabe, R. *et al.* (2012) 'The Therapeutic Relationship and Adherence to Antipsychotic Medication in Schizophrenia', *PLOS ONE*, 7(4), p. e36080. doi: 10.1371/journal.pone.0036080.

McCabe, R. *et al.* (2013) 'Shared understanding in psychiatrist-patient communication: association with treatment adherence in schizophrenia.', *Patient education and counseling*, 93(1), pp. 73–79. doi: 10.1016/j.pec.2013.05.015.

McEvoy, J. P., Hogarty, G. E. and Steingard, S. (1991) 'Optimal dose of neuroleptic in acute schizophrenia. A controlled study of the neuroleptic threshold and higher haloperidol dose.', *Archives of general psychiatry*, 48(8), pp. 739–745. doi: 10.1001/archpsyc.1991.01810320063009.

McGorry, P., Alvarez-Jimenez, M. and Killackey, E. (2013) 'Antipsychotic medication during the critical period following remission from first-episode psychosis: less is more.', *JAMA psychiatry*, 70(9), pp. 898–900. doi: 10.1001/jamapsychiatry.2013.264.

Moilanen, J. *et al.* (2013) 'Characteristics of subjects with schizophrenia spectrum disorder with and without antipsychotic medication - a 10-year follow-up of the Northern Finland 1966 Birth Cohort study.', *European psychiatry : the journal of the Association of European Psychiatrists*, 28(1), pp. 53–58. doi: 10.1016/j.eurpsy.2011.06.009.

Morken, G., Grawe, R. W. and Widen, J. H. (2007) 'Effects of integrated treatment on antipsychotic medication adherence in a randomized trial in recent-onset schizophrenia.', *The Journal of Clinical Psychiatry*, 68(4), pp. 566–571. doi: 10.4088/jcp.v68n0409.

Nykänen, S. *et al.* (2016) 'Use of psychiatric medications in schizophrenia and other psychoses in a general population sample', *Psychiatry research*, 235, pp. 160–168. doi: 10.1016/j.psychres.2015.11.013.

Osterberg, L. and Blaschke, T. (2005) 'Adherence to medication.', *The New England journal of medicine*, 353(5), pp. 487–497. doi: 10.1056/NEJMra050100.

Owen, R. R. *et al.* (2008) 'The Effectiveness of Guideline Implementation Strategies on Improving Antipsychotic Medication Management for Schizophrenia', *Medical Care*, 46(7), pp. 686–691.

Patterson, T. L. *et al.* (2002) 'Medication management ability assessment: results from a performance-based measure in older outpatients with schizophrenia.', *Journal of clinical psychopharmacology*, 22(1), pp. 11–19. doi: 10.1097/00004714-200202000-00003.

Pitschel-Walz, G. *et al.* (2006) 'Psychoeducation and compliance in the treatment of schizophrenia: results of the Munich Psychosis Information Project Study.', *The Journal of clinical psychiatry*, 67(3), pp. 443–452. doi: 10.4088/jcp.v67n0316.

Raskin, S. A. *et al.* (2014) 'Prospective memory in schizophrenia: relationship to medication management skills, neurocognition, and symptoms in individuals with schizophrenia', *Neuropsychology*, 28(3), pp. 359–365. doi: 10.1037/neu0000040.

Semahegn, A. *et al.* (2018) 'Psychotropic medication non-adherence and associated factors among adult patients with major psychiatric disorders: a protocol for a systematic review', *Systematic reviews*, 7(1), pp. 10–10. doi: 10.1186/s13643-018-0676-y.

Seppala, J. *et al.* (2019) 'Mobile Phone and Wearable Sensor-Based mHealth Approaches for Psychiatric Disorders and Symptoms: Systematic Review.', *JMIR mental health*, 6(2), p. e9819. doi: 10.2196/mental.9819.

Seppala, L. J. *et al.* (2019) 'EuGMS Task and Finish group on Fall-Risk-Increasing Drugs (FRIDs): Position on Knowledge Dissemination, Management, and Future Research', *European Geriatric Medicine*, 10(2), pp. 275–283. doi: 10.1007/s41999-019-00162-8.

Smith, R. C., Leucht, S. and Davis, J. M. (2019) 'Maximizing response to first-line antipsychotics in schizophrenia: a review focused on finding from meta-analysis.', *Psychopharmacology*, 236(2), pp. 545–559. doi: 10.1007/s00213-018-5133-z.

Taipale, H. *et al.* (2020) '20-year follow-up study of physical morbidity and mortality in relationship to antipsychotic treatment in a nationwide cohort of 62,250 patients with schizophrenia (FIN20).', *World psychiatry : official journal of the World Psychiatric Association (WPA)*, 19(1), pp. 61–68. doi: 10.1002/wps.20699.

Takeuchi, H. *et al.* (2012) 'Antipsychotic treatment for schizophrenia in the maintenance phase: a systematic review of the guidelines and algorithms.', *Schizophrenia research*, 134(2–3), pp. 219–225. doi: 10.1016/j.schres.2011.11.021.

Thompson, A. *et al.* (2018) 'Maintenance antipsychotic treatment versus discontinuation strategies following remission from first episode psychosis: systematic review', *BJPsych open*, 4(4), pp. 215–225. doi: 10.1192/bjo.2018.17.

Tiihonen, J., Tanskanen, A. and Taipale, H. (2018) '20-Year Nationwide Follow-Up Study on Discontinuation of Antipsychotic Treatment in First-Episode Schizophrenia.', *The American journal of psychiatry*, 175(8), pp. 765–773. doi: 10.1176/appi.ajp.2018.17091001.

Torniainen, M. *et al.* (2015) 'Antipsychotic treatment and mortality in schizophrenia.', *Schizophrenia bulletin*, 41(3), pp. 656–663. doi: 10.1093/schbul/sbu164.

Torous, J. *et al.* (2018) 'Characterizing the clinical relevance of digital phenotyping data quality with applications to a cohort with schizophrenia', *npj Digital Medicine*, 1(1), p. 15. doi: 10.1038/s41746-018-0022-8.

Uchida, H. *et al.* (2011) 'Low dose vs standard dose of antipsychotics for relapse prevention in schizophrenia: meta-analysis', *Schizophrenia bulletin*, 37(4), pp. 788–799. doi: 10.1093/schbul/sbp149.

Uman LS. (2011) Systematic reviews and meta-analyses. J Can Acad Child Adolesc Psychiatry; 20: 57–59.

Veijola, J. *et al.* (2014) 'Longitudinal changes in total brain volume in schizophrenia: relation to symptom severity, cognition and antipsychotic medication', *PloS one*, 9(7), pp. e101689–e101689. doi: 10.1371/journal.pone.0101689.

Velligan, D. *et al.* (2013) 'A randomized trial comparing in person and electronic interventions for improving adherence to oral medications in schizophrenia.', *Schizophrenia bulletin*, 39(5), pp. 999–1007. doi: 10.1093/schbul/sbs116.

Weinmann, S., Janssen, B. and Gaebel, W. (2005) 'Guideline adherence in medication management of psychotic disorders: an observational multisite hospital study', *Acta psychiatrica Scandinavica*, 112(1), pp. 18–25. doi: 10.1111/j.1600-0447.2005.00547.x.

Wilk, J. *et al.* (2006) 'Substance abuse and the management of medication nonadherence in schizophrenia.', *The Journal of nervous and mental disease*, 194(6), pp. 454–457. doi: 10.1097/01.nmd.0000221289.54911.63.

Wilk, J. E. *et al.* (2008) 'Family contact and the management of medication non-adherence in schizophrenia.', *Community mental health journal*, 44(5), pp. 377–380. doi: 10.1007/s10597-008-9139-6.

Wils, R. S. *et al.* (2017) 'Antipsychotic medication and remission of psychotic symptoms 10years after a first-episode psychosis.', *Schizophrenia research*, 182, pp. 42–48. doi: 10.1016/j.schres.2016.10.030.

Wunderink, L. *et al.* (2007) 'Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: relapse rates and functional outcome.', *The Journal of clinical psychiatry*, 68(5), pp. 654–661. doi: 10.4088/jcp.v68n0502.

Wunderink, L. *et al.* (2013) 'Recovery in Remitted First-Episode Psychosis at 7 Years of Follow-up of an Early Dose Reduction/Discontinuation or Maintenance Treatment Strategy: Long-term Follow-up of a 2-Year Randomized Clinical Trial', *JAMA Psychiatry*, 70(9), pp. 913–920. doi: 10.1001/jamapsychiatry.2013.19.

Zhou, Y. *et al.* (2018) 'Dose reduction of risperidone and olanzapine can improve cognitive function and negative symptoms in stable schizophrenic patients: A single-blinded, 52-week, randomized controlled study.', *Journal of psychopharmacology (Oxford, England)*, 32(5), pp. 524–532. doi: 10.1177/0269881118756062.

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	▪ 6 mental health centers, 30 medical records in each, 14 prescribers ▪ 3 years 1990-1994. Mirror-image design: 18-item scale to assess baseline vs. post-training prescriber fidelity at four-month intervals over a period of 30 months. ▪ Prescriber education: designated trainers at baseline and annually focused on medication algorithms and symptom ratings in Medication Management Approaches in Psychiatry (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 ▪ Post-training 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 centers under study not described in detail
Maples et al 2012	▪ 325 patients (schizophrenia spectrum and bipolar disorders) and 345 patients in comparison group ▪ 2 years (12 months before enrollment, 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 2 patient groups ▪ Focus mainly on continuity of care ▪ Potential residual confounding by diagnosis, site and indication ▪ No measures of adherence

Dose tapering studies			
Carlton et al 2008	▪ 3 controlled trials with 223 participants diagnosed with first- or second-episode schizophrenia between 1970s-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
Isohanni 1983 Isohanni 1993	▪ Annual neuroleptic doses of developing therapeutic community (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 1965-1982: 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 vs 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	108 first-episode non-affective psychosis cases in Open Dialogue (OD) model, 1783 controls from registers having treatment as usual (TAU). ▪ Median follow-up 19-20 years, study years from mid-1990s to 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	▪ 236 inpatients were randomly assigned to intervention or routine care. ▪ 2 years follow-up 1990-1994 ▪ Intervention was 8 psychoeducational sessions to patients and their families over a period of 4 to 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
Morken et al 2007	▪ Integrated vs standard treatment for 50 patients between 1992-1999 ▪ 2 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

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 month 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 are 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