In search of appropriate antipsychotic polypharmacy in schizophrenia spectrum disorders

Marc Lochmann van Bennekom

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True polypharmacy is the skillful combination of remedies

William Osler[1]

[1] *In: Bean RB, Osler Sir W: Aphorisms: from his bedside teaching and writings. Springfield, Ill: Charles C Thomas Publisher: 1951*

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Chapter 1

Introduction

Introduction

In my first job as a resident at a psychiatric outpatient clinic in the late 1980s, I still remember very well how I felt when I filled my first prescription for a psychiatric medication. It was a selective serotonin reuptake inhibitor (SSRI) that I prescribed for a middle-aged woman with a depressive disorder, who had never been prescribed psychiatric medications before. When she left my office, I felt insecure about the appropriateness of my choice to start medication in this until then medication-naive patient, thereby causing significant changes in her neurobiology that could disrupt homeostasis. Trying to reassure myself with the prevailing view of depression at the time, that her neurobiology already might have been disturbed by the depression, and prescribing an SSRI could help restore this, I was concerned about the possible negative consequences that the medication that I prescribed could bring in the next weeks. When she came back to see me two weeks later, I was relieved that she had noticed little or no side effects, but unfortunately, her depression had not improved much either.

Years later, during my first job as a psychiatrist in an acute inpatient clinic, I saw many patients who were prescribed multiple psychiatric medications for one or several psychiatric conditions, often in combination with medications because of physical conditions. And although in some cases this seemed sensible, in other cases, it seemed to reflect the practitioner's painstaking efforts to improve the patient's condition. And again, I was concerned about the balance of benefits and harms of this polypharmacy on the patient's condition. That is when my interest in polypharmacy in psychiatry arose.

Pharmacotherapy in psychiatry

The history of pharmacotherapy in psychiatry is long but has changed markedly in the 1950s. Until then, patients with severe psychiatric disorders were hospitalized and treated with chemical agents (e.g., opioids, caffeine, bromine, barbiturates, acetylcholine, and insulin) in addition with interventions like bed rest, wrapping in damp cloths, prolonged bathing, fixation, and isolation. In the 1950s, the serendipitous discovery of the beneficial effects of some existing general medications when used in psychiatry, such as lithium, chlorpromazine, and imipramine, revolutionized the treatment of patients with severe psychiatric disorders by significantly reducing symptoms and improving social functioning. Since the 1990s, second and third generation antipsychotics and new antidepressants were developed, that attributed to better tolerability rather than better efficacy, still leaving patients with treatment refractory symptoms that not sufficiently responded to a single psychotropic agent.

Polypharmacy

Polypharmacy has a long history, dating back at least 2000 years to Mithridates, King of Pontus (120 - 63 B.C.), who resisted the supremacy of the Roman Empire in several wars and tried to prepare a universal antidote by combining many substances in one formulation to protect himself from being poisoned (Aronson, 2004). In PubMed, the electronic resource for searching and retrieving biomedical and life sciences literature, the first reference on the subject with a word of caution dates back more than 150 years (Upton, 1873), highlighting the early controversy surrounding this treatment strategy.

There are many definitions of polypharmacy with differences in the number of medications and the duration of the combined prescription, which complicates scientific research and the comparison of outcomes (Masnoon et al., 2017). Basically, polypharmacy can be described as the concurrent administration of two or more different medications to the same patient. It can be somewhat arbitrarily divided into minor polypharmacy (concurrent use of two to four different medications) and major polypharmacy (concurrent use of five or more different medications), because as the number of medications increases beyond five, the risk of adverse effects due to drug-drug interactions, including the associated risk of hospitalization, increases significantly (Leendertse et al., 2008; Masnoon et al., 2017). Different terms for polypharmacy are used in literature, e.g., polytherapy, adjunctive therapy, combination therapy, co-therapy, add-on therapy or augmentation therapy. These different terms and definitions hamper scientific research in the field.

Polypharmacy is common in general medical practice, with global prevalence rates of approximately 30%, 62%, and 57% for community-dwelling, hospitalized, and institutionalized patients, respectively (Januario et al., 2023). Combinations of medications are prescribed in an attempt to improve disease management of complex single or multiple medical conditions, but can result in increased risk of drug-drug interactions, adverse effects, inappropriate dosing, and medication and/or dose escalation in case of inappropriate polypharmacy (Molokhia and Majeed, 2017).

The word "poly" in polypharmacy refers to both "many" (as in polyneuropathy, a disorder of many nerves) and "too many" (as in polydactyly, an abnormality characterized by too many fingers). Polypharmacy can therefore mean both “many medications” and “too many medications”, making it both a quantitative and qualitative concept, with the latter implying inappropriate or irrational use of multiple medications (Aronson, 2004). While historically it has been a term

with mostly negative connotations, there is now a growing recognition that polypharmacy is not necessarily bad, but should be judged primarily on its quality, of which the number of different medications prescribed to a patient is only one aspect, along with the efficacy and safety of the combination. Polypharmacy is likely to be considered more rational and appropriate when used judiciously in patients with multimorbidity (e.g., in the elderly), or in diseases with a known cause (pathoetiology) and/or physiological changes (pathophysiology) that support multiple mechanisms of action, such as cancer and hypertension.

Psychiatric polypharmacy

As in general medicine, the history of psychiatric polypharmacy runs parallel to the development and availability of psychiatric medications, with psychiatrists attempting to treat refractory psychopathological symptoms or comorbid conditions with combinations of psychotropics medications. Psychiatric polypharmacy can be described as the use of two or more psychiatric medications by a patient for one or more psychiatric disorders (National Association of State Mental Health Program Directors, 2001). It is increasing worldwide in several psychiatric disorders such as schizophrenia, mood disorders, and borderline personality disorder, including associated psychiatric comorbidity (Sarkar, 2017). In the United States, up to 60% of patients are prescribed two or more psychotropic medications and 33% are prescribed three or more psychotropic medications (Mojtabai and Olfson, 2010). In a Hungarian study, 33% of psychiatric patients were prescribed more than five medications, including medications for somatic conditions (Viola et al., 2004). Psychiatrists' attitudes toward polypharmacy may be affected by cultural differences, resulting in different prevalence rates in different regions of the world (Nakagami et al., 2021). Unlike polypharmacy in general medicine, which primarily affects the elderly, psychiatric polypharmacy affects patients of all ages, including children and adolescents (Sarkar, 2017).

To better describe the impact and appropriateness of psychiatric polypharmacy in greater detail, the *National Association of State Mental Health Program Directors* defined five categories of psychiatric polypharmacy (see table 1) (National Association of State Mental Health Program Directors, 2001).

Table 1 Categories of psychiatric polypharmacy according to the National Association of State Mental Health Program Directors (NASMHPD, 2001)

Same-class polypharmacy	The use of more than one medication from the same medication class* (e.g., two selective serotonin reuptake inhibitors).
Multi-class polypharmacy	The use of full therapeutic doses of more than one medication from different medication classes for the same symptom cluster (e.g., the use of lithium along with an antipsychotic).
Adjunctive polypharmacy	The use of one medication to treat the side effects or secondary symptoms of another medication from a different medication class (e.g., the use of trazadone along with bupropion for insomnia).
Augmentation polypharmacy	The use of one medication at a lower-than-normal dose along with another medication from a different medication class at its full therapeutic dose, for the same symptom cluster (e.g., the addition of a low dose of haloperidol in a patient with a partial response to risperidone). Or the addition of a medication that would not be used alone for the same symptom cluster (e.g., the addition of lithium in a person with major depression who is currently taking an antidepressant).
Total polypharmacy	The total count of medications used in a patient, or total medication load. Consideration of total polypharmacy should include prescription medications, over-the-counter medications, alternative medical therapies, and elicit pharmacological agents

**Medication class refers to medications with similar mechanisms of action*

Preskorn and Lacey formulated criteria for rational combination therapy in psychiatry that can be used by clinicians to evaluate publications on polypharmacy in psychiatry and translate them into clinical practice (Preskorn and Lacey, 2007):

1. Knowledge that the combination has a positive effect on the pathophysiology or pathoetiology of the disorder.
2. Convincing evidence that the combination is more effective, including more cost-effective, than monodrug therapy.
3. The combination should not pose significantly greater safety or tolerability risks than monotherapy:
   a. Drugs should not have narrow therapeutic indices.
   b. Drugs should not have poor tolerability profiles.
4. Drugs should not interact both pharmacokinetically and pharmacodynamically.
5. Drugs should have mechanisms of action that are likely to interact in a way that augments response.
6. Drugs should have only one mechanism of action.
7. Drugs should not have a broad-acting mechanism of action.
8. Drugs should not have the same mechanism of action.

9. Drugs should not have opposing mechanisms of action.
10. Each drug should have simple metabolism.
11. Each drug should have an intermediate half-life.
12. Each drug should have linear pharmacokinetics.

However, the conceptual basis for combining medications in psychiatric conditions, particularly for difficult-to-treat symptoms, is still generally lacking. Satisfactory explanatory models based on pathophysiology, let alone pathoetiology, are not available for most psychiatric disorders. Consequently, there are no known different mechanisms of action, which limits the ability to develop effective combination strategies when monotherapy is insufficient. Data on cost-effectiveness of combinations of psychiatric medications are also generally sparse. And although the other criteria formulated by Preskorn & Lacey, such as efficacy, safety, low risk of drug-drug interactions, narrow and not opposing mechanisms of action, and no complex pharmacodynamic and pharmacokinetic properties of the combined medications are important and helpful, there is still an urgent need for additional criteria to help clinicians distinguish between more and less appropriate polypharmacy in psychiatry (Preskorn and Lacey, 2007; Nakagami et al., 2021; Ordak et al., 2022; Hughes, 2021; Zigman and Blier, 2012).

Antipsychotic polypharmacy in schizophrenia and other psychotic disorders

Although up to now the pathophysiology of schizophrenia (and other psychotic disorders) has not been elucidated, the dopamine hypothesis and its subsequent elaborations have been the dominant explanatory model in the past several decades, although there is increasing recognition of the heterogeneity of the disorder (Keshavan et al., 2011). The dopamine hypothesis proposes that dysregulation and imbalance of dopaminergic function in the brain is a key mechanism in the pathophysiology of schizophrenia, with striatal presynaptic hyperdopaminergia involving D_2 receptors underlying psychotic symptoms and cortical hypodopaminergia involving D_1 receptors underlying cognitive symptoms (McCutcheon et al., 2020; Kaar et al., 2020). Based on this hypothesis, reducing striatal hyperdopaminergia is considered to be the mechanism of action in treating positive symptoms of schizophrenia, with all approved antipsychotic medications intervening on dopaminergic transmission, generally by blocking 60-80% of postsynaptic dopamine D_2 receptors in the striatal region of the brain (Kaar et al., 2020). Interestingly, clozapine, an antipsychotic medication with superior efficacy in patients with treatment-resistant schizophrenia (i.e., patients with schizophrenia who have persistent moderate to severe positive, negative and/

or disorganized symptoms and social dysfunction, despite at least two adequate trials with antipsychotic medications), has a weak affinity for the D_2 receptor and a much higher affinity for several other receptors, such as the serotonergic, adrenergic and histaminergic receptors (Meltzer, 1997; Meltzer, 1994). This suggests that alterations in other neurotransmission pathways may also play a role in the pathophysiology, but it is suggested that these pathways may regulate the striatal presynaptic dopamine release "upstream", resulting in decreased postsynaptic dopamine receptor activation "downstream" (Kaar et al., 2020). However, there is no solid evidence for an antipsychotic effect for treatments with agents affecting these pathways per se. Neuroinflammation and increased oxidative stress have also been implicated in the pathophysiology of schizophrenia, but their potential mechanisms of action are not well understood, and no anti-inflammatory or antioxidative medication is approved as an antipsychotic.

Guidelines recommend that patients with a psychotic disorder be treated with a single antipsychotic, but this is not always effective. Treatment-resistant symptoms persist in approximately 30 to 40% of patients despite multiple antipsychotic monotherapies (Lally et al., 2016; Meltzer, 1997; Diniz et al., 2023), prompting clinicians to consider alternative treatments. New agents modulating dopaminergic and, more recently, glutamatergic and muscarinic neurotransmission are under investigation but are not yet (Kaar et al., 2020; McCutcheon et al., 2020), or only very recently (Kaul et al., 2024), available for clinical use. Therefore, antipsychotic polypharmacy (APP) with two or more antipsychotics that block striatal postsynaptic dopamine D_2 receptors is the most commonly used strategy to treat persistent psychotic symptoms. APP can be defined as the concurrent use of two different antipsychotic medications by a patient and is an example of same-class polypharmacy. Several definitions are used in the literature, differing mainly in the duration of APP, varying from more than 30, more than 60 or even more than 90 days, to exclude temporary APP due to a trajectory of cross-titration switching of antipsychotics (Foster and King, 2020). Reported prevalence rates of APP vary due to differences in methodology, definitions, and regional differences around the world (Foster and King, 2020), but in a meta-analysis of primarily cross-sectional studies, APP has been common in all regions of North America, Europe, Asia, and Oceania over the past several decades, with a pooled median prevalence of approximately 20% (Gallego et al., 2012). Theoretically, it aims at increasing the postsynaptic dopamine D_2 receptor blockade, typically by combining an antipsychotic that has weak affinity for the D_2 receptor with an antipsychotic with high affinity for the D_2 receptor. However, the evidence found in individual studies and meta-analyses for the efficacy of APP is inconclusive, which may be partly explained by small sample

size of prospective the studies investigating these often severely ill psychotic patients, differences in definitions, differences in study quality, differences in the combinations of antipsychotics studied, differences in the patients included (e.g., level of treatment refractoriness), and differences in the outcome measures (e.g., effects on positive symptoms only, effects on positive and negative symptoms, or effects on psychiatric hospitalizations) (Ortiz-Orendain et al., 2017; Galling et al., 2017; Tiihonen et al., 2019; Greer et al., 2023; Correll et al., 2009; Paton et al., 2007; Taylor and Smith, 2009; Taylor et al., 2012; Wang et al., 2010). From a conceptual point of view, given the criteria for rational (appropriate) polypharmacy by Preskorn & Lacey that include targeting multiple pathophysiologic mechanisms of action (Preskorn and Lacey, 2007), there is also little support for the rationality of this form of polypharmacy. Nevertheless, there is inconclusive evidence for efficacy of APP from meta-analyses (Galling et al., 2017; Taylor and Smith, 2009; Taylor et al., 2012; Paton et al., 2007; Correll et al., 2009; Barbui et al., 2009), and some recent real-world studies have found APP to be more effective than antipsychotic monotherapy in reducing psychiatric hospitalizations, cardiovascular hospitalizations, and mortality (Tiihonen et al., 2019; Katona et al., 2014), although not consistently (Korkmaz et al., 2024). In addition, a review and meta-analysis of five discontinuation studies found some evidence that continuation of APP may be associated with a lower number of participants leaving the study early due to inefficacy (Bighelli et al., 2022), which may suggest greater efficacy of APP compared with antipsychotic monotherapy, although interestingly, the level of psychopathology did not differ between both groups. However, in a recent extended update that included three additional studies, there was no difference in all-cause discontinuation or in efficacy-related discontinuation between both groups, and there was a trend toward a reduction in psychopathology scores in the monotherapy group (Kohler-Forsberg et al., 2024). Nevertheless, in the included discontinuation studies, a proportion of patients could not be successfully tapered to antipsychotic monotherapy, and when analyzed at a more individual level, there is some evidence that discontinuation to monotherapy may be less successful in more treatment-resistant patients (Borlido et al., 2016; Matsui et al., 2019).

These inconclusive results from meta-analyses on efficacy of APP, meta-analyses on conversion from APP to antipsychotic monotherapy, and real-world studies warrant more research to identify patients that do and do not benefit from APP.

First do no harm

In medicine in general, and in pharmacotherapy in particular, it is essential that the benefits of a treatment outweigh the potential risks. The Latin axiom "*primum*

non nocere" (first, do no harm), associated with the Hippocratic Oath but probably attributed to the 17th-century English physician Thomas Sydenham (1624-1689), states that physicians should not cause physical or moral harm to a patient during treatment and should abstain when in doubt ("*in dubio abstine*"). For the development and marketing of new individual medications, safety and efficacy are ensured within the framework of international regulations for the registration of new medicines, which include high-quality efficacy studies and a comprehensive risk assessment (Zhang and Winston, 2024). However, when medications are combined, as in APP, pragmatic clinical application often precedes thorough research on efficacy and safety. On the one hand, this is understandable because APP is often prescribed to patients with severe psychotic illness who are difficult to enroll in randomized trials in sufficient numbers. On the other hand, it also requires additional efforts to thoroughly investigate the benefits and risks of APP.

Summary

Antipsychotic polypharmacy, like polypharmacy in general, is an unclearly defined concept, which complicates scientific research. Besides in a process of cross-titration switching of antipsychotics, APP is mainly used in an attempt to treat refractory psychotic symptoms, which apparently persist in up to 20% of patients treated for schizophrenia. In this context, a useful definition of APP is the simultaneous use of two or more different antipsychotic medications by a patient for more than 60 days. This definition largely excludes temporary appropriate APP due to cross-over antipsychotic switching. When evaluating the benefits and harms of APP, it is important to assess the quality of the polypharmacy prescription, which is determined by the efficacy and safety of the combination, rather than the number of medications involved.

The use of polypharmacy in psychotic disorders may be more justified when the underlying pathoetiology and pathophysiology is known and when the combination of medications acts on multiple mechanisms of action. In psychotic disorders, the most robust theoretical paradigm is the dopamine hypothesis, which posits striatal hyperdopaminergica and cortical hypodopaminergica. Postsynaptic blocking of striatal D_2 receptors is considered a necessary, although not always sufficient, mechanism of action for the treatment of psychotic symptoms. However, no other mechanisms of action impacting aberrant dopaminergic transmission have been identified to support the rationality and appropriateness of APP. Existing guidelines for the treatment of schizophrenia and other psychotic disorders recommend the use of APP only as a last resort for patients with treatment-resistant symptoms who have already received adequate treatment with two different antipsychotics and

clozapine. However, when reviewing the scientific literature, there emerges some evidence that APP may be beneficial in some patients with psychotic disorder, but several methodological issues in studying this heterogeneous and often severely ill population make it difficult to draw firm conclusions about the added value of APP compared with antipsychotic monotherapy. This thesis aims to provide more personalized evidence to assess who may or may not benefit from APP, with the intention of contributing to a more appropriate use of this treatment.

This thesis

Aim and research questions

The main objective of this thesis is to examine what may contribute to the appropriate use of APP in patients with psychotic disorders. In the absence of clear guidelines, we are interested in the extent to which psychiatrists agree on the appropriateness or inappropriateness of prescribing psychiatric polypharmacy, the evidence for the rationality and thus appropriateness of APP, the possibility of reducing inappropriate APP, and identifying characteristics of patients who may benefit from APP that can guide clinical decision making.

Outline

In **Chapter 2** we examine the extent to which psychiatrists agree in judging the rationality of medication prescriptions, using the intra-class correlation coefficients of these judgments in five clinical vignettes with varying levels of polypharmacy. If agreement decreases when the number of medications prescribed increases, this may indicate that the quality of pharmacotherapy may be compromised as medication regimens become more complex. In **Chapter 3,** a systematic review summarizes the evidence for the rationality of APP based on the criteria of Preskorn & Lacey (Preskorn and Lacey, 2007), in terms of the underlying neurobiological mechanism of action, efficacy, tolerability, and cost-effectiveness. In **Chapter 4**, we report on a serial intervention study in which we examined whether a personalized e-mail intervention with guideline referral contributes to a reduction in antipsychotic polypharmacy. If so, this may indicate that the intervention supports a higher quality of antipsychotic prescribing. **Chapter 5** describes a prospective observational study in which we followed a cohort of 55 patients that were prescribed APP and asked prescribers about the indication at initiation and at 60 days. Clarity about this longitudinal course of APP can provide insight into when and why APP is discontinued and the extent to which persistent APP is a deliberate choice. In **Chapter 6** we report the results of an individual patient data meta-analysis (IPDMA) that attempts to identify subgroups of patients who do or do not

benefit from antipsychotic polypharmacy, based on the individual patient data from ten RCTs into the efficacy of APP. Compared to a traditional study-level meta-analysis, an IPDMA offers important advantages for detecting effect moderators, including increased granularity and statistical power (Hannink et al., 2013). **Chapter 7** concludes with a summary, conclusions, a general discussion, and clinical recommendations.

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1

Chapter 2

Poor Agreement amongst Psychiatrists Assessing Rationality in Five Cases of Psychiatric Polypharmacy

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Introduction

Psychiatric polypharmacy (the concurrent administration of two or more psychotropics to one patient) is common practice in treatment of psychiatric patients and is on the rise in the last decades (Rittmannsberger, 2002; Botts et al., 2003). It is practiced for several reasons such as treatment refractoriness, co-morbidity, alleviation of symptoms refractory to treatment, reduction of side effects of the primary drug and attempts to attain early onset of action (Dufresne, 1995). Drawbacks of the strategy are an increase of side effects, drug-drug interactions, non-compliance and the prescription of sub-therapeutic dosages (Dufresne, 1995; Nayak, 1998). Moreover, robust scientific evidence demonstrating the efficacy of polypharmacy as treatment option is lacking for almost every psychiatric disorder (Freudenreich and Goff, 2002; Zarate and Quiroz, 2003; Zanarini, 2004; Viola et al., 2004). Attempts have been made to guide clinicians in practicing rational polypharmacy (Wolkowitz, 1993; Post et al., 1996; Reus, 1993), but no scientific data are available on what polypharmacy regimens psychiatrists consider rational and what not, and to which extent psychiatrists would agree on their judgment in the same case. As a first step to elucidate this subject, we studied inter-rater reliability of twenty psychiatrists globally assessing rationality of psychiatric polypharmacy in five vignettes.

Table 1 Descriptive features of five vignettes with psychiatric polypharmacy.

Vignette	**1**	**2**	**3**
Age	39	35	50
Gender	M	M	F
Classifi-cation (DSM-IV)	Schizophrenia, paranoid type	Major depressive disorder, single episode	Major depressive disorder with melancholic features
Setting	Inpatient	Outpatient	Outpatient
Duration of illness	11 years	2 weeks	> 7 years
Prescribed psycho-tropics	1. Clozapine 550 mg/d 2. Fluspirilene 6 mg/w 3. Temazepam 20 mg/d 4. Oxazepam 100 mg/d + 50-100 mg/d prn 5. Biperiden 2 mg/d	1. Paroxetine 20 mg/d 2. Temazepam 20 mg/d	1. Amitriptyline 150 mg/d 2. Lithium-carbonate 800 mg/d 3. Riperidone 2 mg/d

Case report

We invited 29 psychiatrists from three psychiatric institutions (two psychiatric hospitals and one academic psychiatric department) to participate in the study. Participants were registered psychiatrists, at least 50% of their working time treating adult psychiatric patients. They were asked to assess rationality of medication prescription in five vignettes, describing actual case histories with psychiatric polypharmacy. Vignettes (three inpatients and two outpatients from an institute for mental health) were selected by the first author out of a cross-sectional sample of 80 clinical patient histories involving psychiatric polypharmacy to represent some variety in diagnosis and number of prescribed drugs. Apart from the information presented in Table 1, the vignettes contained detailed information on indication, treatment duration, blood levels and clinical effect of each actual psychotropic as well on prior psychopharmacological interventions and clinical functioning (in 153 – 409, average 308 words). Level of rationality was rated on a 100 mm visual analogue scale (VAS), ranging from 0 (extremely irrational) to 100 (extremely rational).

	4	**5**
	33	34
	F	M
	Anxiety disorder NOS	Schizoaffective disorder
	Inpatient	Inpatient
	5 years	> 1 year
	1. Haloperidol 4 mg/d 2. Clomipramine 150 mg/d 3. Propranolol 80 mg/d 4. Oxazepam 150 mg/d + 50 mg/d prn 5. Levomeproma-zine 25 mg/d prn	1. Haloperidol 7.5 mg/d 2. Carbamazepine 800 mg/d 3. Temazepam 20 mg/d 4. Paroxetine 20 mg/d 5. Oxazepam 10 mg/d + 25 mg/d prn 6. Promethazine 25 mg/d prn 7. Biperiden 4 mg/d prn

Results and discussion

Twenty out of 29 psychiatrists (69%) returned the rating form. Four (20%) stemmed from the academic setting, 16 (80%) were non-academic. Nine respondents (45%) were working with in- and outpatients, nine (45%) with only inpatients and two (10%) with only outpatients. The mean level of psychiatric experience was 13.8 years (range: 1-30 years). Respondents rated all five cases, resulting in 100 ratings. Table 2 shows data on VAS-ratings per vignette. Inter-rater reliability between all raters over all vignettes, computed with the Intra-class Correlation Coefficient (ICC, two-way random effects model, using an absolute agreement definition) is a modest 0.109 (95% CI = 0.006-0.295; $p < 0.005$).

Table 2 VAS-ratings on rationality of psychiatric polypharmacy per vignette

	Mean VAS score[1]	Range (min-max)	SD
Vignette 1	37	11 – 77	19
Vignette 2	85	42 – 97	12
Vignette 3	63	30 – 96	19
Vignette 4	52	6 – 90	25
Vignette 5	42	8 – 72	20

[1]scores in mm, 0 = extremely irrational, 100 = extremely rational

Our data show that judgments on rationality of psychiatric polypharmacy are quite heterogeneous and inter-rater reliability is poor, barely exceeding agreement by chance. This finding is in line with a study from 1981 by Gillis et al., demonstrating agreement below chance levels between 70 psychiatric staff members on assigning appropriate classes of psychotropic drugs, specific drugs and dosage levels in 40 hypothetical psychiatric cases (Gillis et al., 1981).

Our observations are preliminary due to small sample size. Further limitation is the unstable inter-rater reliability of the VAS scale demonstrated in some studies (de Jong et al., 2005). Finally, our study design provides no information about processes affecting clinician's appraisal of these polypharmacy prescriptions.

Clinicians are stimulated to adhere to accepted guidelines for the treatment of psychiatric disorders in order to practice evidence-based medicine. Ito et al. showed that the use of multiple medications and excessive dosing amongst others was influenced by the psychiatrist's skepticisms towards the use of evidence-based guidelines or algorithms (Ito et al., 2005). However, existing guidelines and

algorithms have relatively modest sections on refractory psychiatric disorders and co-morbidity. In an effort to describe the impact and appropriateness of polypharmacy in greater detail the Medical Directors Council of the National Association of State Mental Health Program Directors (NASMHPD) (National Association of State Mental Health Program Directors, 2001) distinguish five categories of polypharmacy: same-class polypharmacy, multi-class polypharmacy, adjunctive polypharmacy, augmentation and total polypharmacy. Yet, the NASMHPD acknowledges that defining polypharmacy as occurring in one of the above categories only partially addresses the complexities inherent in polypharmacy.

There is a need for more research on appropriate pharmacological treatment of refractory psychiatric disorders and co-morbidity, knowledge that should be embodied in existing clinical guidelines in order to prevent inappropriate psychiatric polypharmacy. For clinicians it brings the obligation to take notice of available guidelines and adhere to them as much as possible.

Conclusions

In this sample, we found poor agreement between psychiatrists' judgments on the rationality of psychiatric polypharmacy, possibly reflecting a problem in quality of treatment of psychiatric patients. Conclusions are preliminary due to small sample size, and our results need replication.

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Chapter 3

Antipsychotic Polypharmacy in Psychotic Disorders: A Critical Review of Neurobiology, Efficacy, Tolerability and Cost Effectiveness

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Summary

Objective: To review the scientific evidence for neurobiological rationale, efficacy, tolerability and cost effectiveness of antipsychotic polypharmacy (APP).

Data sources: A systematic literature search of Medline, Embase, Ovid and the Cochrane Database of Systematic Reviews until April 2012 was carried out.

Results: Theories behind APP have only modest pre-clinical and clinical evidence. We found limited statistical evidence supporting modest efficacy of APP in patients with psychotic symptoms refractory to clozapine. APP is associated with increased mortality, metabolic syndrome, decreased cognitive functioning, high dose prescription and non-adherence. It brings up extra costs, lacking evidence for cost-effectiveness.

Conclusions: Pre-clinical studies underpinning neurobiological hypotheses in APP are lacking. Evidence supporting efficacy of APP is limited with modest beneficial clinical relevance. APP is associated with several serious adverse effects and increased health costs. In the absence of more convincing pre-clinical support and clinical evidence we advise to adhere to existing guidelines and limit combinations of antipsychotics (in consideration with other pharmacotherapeutic, somatic and psychotherapeutic options) to patients with clozapine-refractory psychosis in well-evaluated individual trials that might need 10 weeks or more.

Introduction

Antipsychotic polypharmacy (APP) is the concurrent use of two or more different antipsychotic agents by one patient. According to the definitions of the consensus meeting of the US *National Association of State Mental Health Program Directors* (National Association of State Mental Health Program Directors, 2001) it is an example of same class polypharmacy and, depending on prescribed co-medication, a more or less substantial part of total polypharmacy in a patient.

Prevalence of APP is high, considering guidelines advocating antipsychotic monotherapy and limiting APP as an option in clozapine-refractory psychotic patients (Lehman et al., 2004; Moore et al., 2007; National Institute for Clinical Excellence, 2009). Relative short term (<2 months) APP is reported in 5 – 42% (Broekema et al., 2007; Chakos et al., 2006) and long term (≥1 year) APP in approximately 13% of patients on antipsychotic treatment (Barbui et al., 2006). In a large study by Gallego and colleagues, the overall prevalence rate of APP across decades and global regions was 19.6%. They also found that APP since the 1980s has increased in the US from 12.7% to 17% and Oceania from 2% to 17%, fluctuated in Europe between 19% and 24%, but markedly decreased in Asia from 55.5% to 19.2% (Gallego et al., 2012). Besides differences in region and year of study, the large variety in prevalence rates across studies is also due to methodological differences such as setting, in- or exclusion of low potency antipsychotics and as-required ('p.r.n.') antipsychotics, and duration of antipsychotic co-prescription thus ruling in or out APP during cross-over switching of antipsychotics.

Findings that more than one third (Howes et al., 2012) or even up to 65% (Taylor et al., 2012) of patients on clozapine have previously received non-clozapine APP, and that in only 4% of patients on APP a previous trial of clozapine was commenced (Langan and Shajahan, 2010) suggest that adherence to existing guidelines is insufficient. This may contribute to an inappropriate delay of clozapine treatment lasting up to 4 – 5 years (Howes et al., 2012; Taylor et al., 2003). Short-term APP can be appropriate while cross-tapering in a process of switching antipsychotics. Persistent APP can be part of a pharmacotherapeutic strategy, but also the unintended result of unfinished cross-titration in a process of switching antipsychotics (Chong and Remington, 2000; Sernyak and Rosenheck, 2004; Stahl, 1999).

High APP prescribers have more clinical experience, less concern about APP and are more likely to prescribe a preferred combination of antipsychotics, although no overall preferred strategy emerged. Both high and low APP prescribers have

'inherited' most of their APP cases from their colleagues and are reluctant to switch patients to antipsychotic monotherapy (Correll et al., 2009). Psychiatrists who are sceptical towards evidence-based guidelines or algorithms more often use APP and prescribe excessive doses of antipsychotics (Ito et al., 2005). The most important clinical reasons for APP are refractory psychotic symptoms by increasing D_2-antagonism, reducing negative symptoms (dominantly by adding an atypical to a conventional antipsychotic), reducing multi-class polypharmacy, and extrapyramidal symptoms (Sernyak and Rosenheck, 2004). Incidentally it is used to manage side effects of the primary antipsychotic agent (Fleischhacker et al., 2010; Shim et al., 2007). Patient factors associated with APP are long duration of illness, frequent previous psychiatric hospitalizations and marked thought disorders at admission (Janssen et al., 2004).

Important building blocks of high-quality, effective, and safe health care delivery are basic neurobiological science, its translation into clinical research on efficacy, effectiveness and tolerability and finally the adoption in clinical guidelines that can be implemented in a cost-effective way (Dougherty and Conway, 2008; Honer et al., 2009)(Dougherty and Conway, 2008; Honer et al., 2009). There are serious concerns that in APP this is not the case, making it 'psychiatry's dirty little secret' (Stahl, 1999). In this paper, we review the scientific evidence for 1) the neurobiological mechanisms of APP, 2) its efficacy, 3) tolerability and 4) cost-effectiveness. We conclude with an integrative discussion, give clinical suggestions, and propose directions for future research.

Methods

Medline, Embase, Ovid and the Cochrane Database of Systematic Reviews were searched until April 2012. The search was performed by using the following search terms: schizophrenia AND antipsychotic* AND "antipsychotic polypharmacy" OR "antipsychotic combination" OR "antipsychotic augmentation" OR "antipsychotic add on" OR "antipsychotic co-prescription" in title and/or abstract. Limitations were set to humans and (young) adults/middle aged. Out of the resulting 177 articles, relevant publications were extracted using following search terms:

- For data on neurobiological rationale: "neurobiology" OR "neurobiological rationale" OR "mechanism of action"
- For data on efficacy: "efficacy" OR "effectiveness" AND "systematic review" OR "meta-analysis".

- For data on tolerability: "tolerability" OR "drug safety" OR "adverse drug event"
- For data on cost-effectiveness: "cost effectiveness" OR "cost benefit analysis"

Reference lists from retrieved articles were reviewed for relevant studies to complete this literature search.

Results

Neurobiological mechanism

Combining antipsychotics should be based on neurobiological knowledge of mechanism of action. The neurobiological rationale of combining antipsychotics is mostly based on one or more of the following hypotheses (Freudenreich and Goff, 2002):

1. Dopamine hypothesis
2. Serotonin hypothesis
3. Receptor binding profiles

Dopamine hypothesis

The dopamine hypothesis postulates that psychotic symptoms are the result of mesolimbic dopaminergic hyperactivity. Antipsychotics have D_2-antagonistic properties, thus diminishing mesolimbic hyperdopaminergic state and reducing psychotic symptoms (Meltzer and Stahl, 1976). It is assumed that antipsychotics are most effective and have the least side effects with D_2 receptor occupancy of 70-80%. Combination of an antipsychotic with relative weak D_2 receptor binding properties (like clozapine or quetiapine) and an agent with strong D_2 binding (like haloperidol or risperidone) or selective D_2 binding (like sulpiride or amisulpride) theoretically can result in optimal 70-80% D_2 receptor occupancy (Seeman and Tallerico, 1998). Clozapine augmentation studies with sulpiride, amisulpride and risperidone are based on this theory (Anil Yagcioglu et al., 2005; Genc et al., 2007; Shiloh et al., 1997). However, the scientific evidence supporting this neurobiological theory is limited. Preclinical studies investigating the effect of combinations of antipsychotics in animal models are sparse (Honer et al., 2009). There is some pre-clinical evidence for beneficial effect of amperozide (a putative antipsychotic compound) in combination with haloperidol on conditioned avoidance response and food-reinforced lever-pressing tasks in rats, suggesting therapeutic value in the treatment of psychotic disorders (Egbe et al., 1990). In a clinical SPECT study, addition of 4 mg haloperidol in 6 patients using 450-500 mg clozapine daily actually resulted in increased D_2

receptor occupancies from 21.2% (SD 17.1) at baseline to 65.3% (SD 22.6) after 10 weeks in the haloperidol-group (n = 2) compared with 22.8% (SD 8.44) to 21.0% (SD 14) in the control group (n=4), however without significant clinical improvement (Mossaheb et al., 2006). On the other hand, a small clinical MRI study in 5 patients demonstrated that four weeks addition of 4 mg of haloperidol to five patients using 225 – 500 mg clozapine actually resulted in increased D_2 receptor occupancy from 55 to 79%, similar to haloperidol monotherapy (Kapur et al., 2001). The level of D_2 receptor occupancy in the last week was related to the plasma level of haloperidol, rather than to the plasma level of clozapine. This might implicate that in APP the antipsychotic with the weakest D_2 binding (clozapine) is replaced by the agent with the strongest D_2 affinity (Taylor and Smith, 2009). This hypothesis is supported by a SPECT study that found that amisulpride augmentation to clozapine increased D_2 receptor occupancy but not to the extent expected (Matthiasson et al., 2002).

Serotonin hypothesis

Serotonin is thought to play a role in the pathophysiology of schizophrenia. In a highly simplified model, antagonism of the $5HT_{2A}$ receptor blocks the inhibiting effect of the serotonergic system on dopamine release in the medial prefrontal cortex, improving signal-to-noise-ratio and restoring prefrontal cortical functioning with positive effects on cognition and negative symptoms (Di Pietro and Seamans, 2007). Second generation antipsychotics have antagonistic properties on both D_2 receptor and (amongst others) $5HT2_{2A}$ receptor, using this mediating effect. A $5HT_{2A}/D_2$-ratio >1 is typical for these agents (Meltzer et al., 1989). APP consisting of the combination of a first and second-generation antipsychotic drug is based on this serotonin hypothesis in treating negative symptoms. However, we found no in vivo or in vitro studies investigating the combined effect of first and second-generation antipsychotics on prefrontal cortical dopamine balance.

Receptor binding profiles

Theoretically, combining antipsychotics with different receptor binding profiles can be an attempt to mimic the broad receptor binding profile of clozapine, a superior agent in the treatment of refractory positive or negative symptoms (Freudenreich and Goff, 2002). It also can aim to reduce the expression of side effects of each of the individual agents at the same level of cumulative D_2 receptor blocking. However, we found no evidence supporting these hypotheses.

In summary

The overall conclusion is that all these hypotheses on combining antipsychotics are empirically insufficiently supported, lacking robust preclinical or clinical data.

Efficacy

Efficacy of combining antipsychotics needs to be demonstrated in high quality research, preferably systematic reviews and meta-analyses of randomised controlled trials. Therefore, we limited our literature search to these publication types, which yielded 7 systematic reviews. We excluded one review (Cipriani et al., 2009) that did not have a control condition of antipsychotic monotherapy, leaving 6 reviews analysing 39 publications on efficacy of APP. These 39 publications consisted of 32 (blinded or unblinded) RCT's studying combinations of clozapine with a second antipsychotic and 7 (blinded or unblinded) RCT's with non-clozapine antipsychotic combinations. Twenty-one of these studies were conducted in Asia, including 17 studies from China. Table 1 provides an overview of the main characteristics of all reviewed publications and the systematic reviews that included them.

Table 1 Main characteristics of all reviewed publications and the systematic reviews that included them.

	Study	Country	DB	PI	n (I/C)	Comparison
RCT's involving clozapine combinations						
1	(Anil Yagcioglu et al., 2005)	Turkey	Y	Y	30 (16/14)	CLZ + RIS vs CLZ
2	(Assion et al., 2008)	Germany	Y	Y	16 (13/3)	CLZ + AMISUL (400/600 mg/d) vs. CLZ
3	(Cha et al., 1999)	China	N	N	200 (100/100)	CLZ + CPZ vs. CLZ
4	(Chang et al., 2008)	Korea	Y	Y	62 (30/32)	CLZ + ARI vs. CLZ
5	(Fleischhacker et al., 2010)	Austria, Finland, France, UK, US	Y	Y	207 (108/99)	CLZ + ARI vs. CLZ
6	(Freudenreich et al., 2007)	US	Y	Y	24 (11/13)	CLZ + RIS vs. CLZ
7	(Friedman et al., 2011)	US	Y	Y	53 (25/28)	CLZ + PIM vs. CLZ
8	(Honer et al., 2006)	Canada, Germany, China, UK	Y	Y	68 (34/34)	CLZ + RIS vs. CLZ
9	(Jia et al., 2000)	China	N	N	50 (26/24)	CLZ + PIP vs. CLZ
10	(Josiassen et al., 2005)	US	Y	Y	40 (20/20)	CLZ + RIS vs. CLZ
11	(Kreinin et al., 2006)	Israel	Y	Y	40 (20/20)	CLZ + AMISUL vs. CLZ
12	(Liu et al., 1996)	China	N	N	63 (31/32)	CLZ + SUL vs. CLZ
13	(Liu and Li, 2001)	China	N	N	64 (32/32)	CLZ + RIS vs. CLZ
14	(Mossaheb et al., 2006)	Austria	Y	Y	6 (2/4)	CLZ + HAL
15	(Muscatello et al., 2011)	Italy	Y	Y	40 (20/20)	CLZ + ARI vs. CLZ
16	(Ni et al., 2001)	China?	N	N	215 (109/106)	CLZ + RIS vs. CLZ
17	(Nielsen et al., 2012)	Denmark	Y	Y	50 (25/25)	CLZ + SER vs. CLZ
18	(Peng et al., 2001)	China?	N	N	66 (32/34)	CLZ + RIS vs. CLZ
19	(Potter et al., 1989)	China	N	Y	37 (20/17)	CLZ + CPZ vs. CLZ
20	(Shiloh et al., 1997)	Israel	Y	Y	28 (16/12)	CLZ + SUL vs. CLZ
21	(Wang et al., 1994)	China	?	N	70 (36/34)	CLZ + SUL vs. CLZ
22	(Weiner et al., 2010)	US	Y	Y	69 (33/36)	CLZ + RIS vs. CLZ
23	(Wu, 2002)	China?	N	N	67 (33/34)	CLZ + RIS vs. CLZ
24	(Xao, 1999)	China?	N	N	41 (20/21)	CLZ + SUL vs. CLZ
25	(Xie and Ni, 2001)	China	Y	?	40 (20/20)	CLZ + RIS vs. CLZ

Dur.	Outcome (+/-)	Included in review by					
		Paton et al., 2007	Barbui et al. 2008	Taylor & Smith, 2009	Correll et al., 2009	Wang et al. 2010	Taylor ea 2011
6w	+ (PANSS)	X	X	X	X		X
6w	- (BPRS) (600 mg + on sec. outcome CGI, GAF, MADRS)			X			X
6w	+ (BPRS)		X				
8w	- (BPRS)			X			X
16w	- (PANSS)			X			X
6w	- (PANSS)		X	X	X		X
12w	- (PANSS)						X
18w	- (PANSS)	X	X	X	X		X
12w	+ (BPRS)		X				
12w	+ (BPRS)	X	X	X	X		X
3w	- (PANSS)		X				
12w	+ (BPRS)		X		X		
10w	- (BPRS)		X				
10w	- (PANSS)			X			X
24w	+ (BPRS, SAPS, SANS)						X
8w	+ (PANSS)		X				
12w	- (PANSS)						X
8w	- (BPRS)		X		X		
8w	- (BPRS)			X	X		X
10w	+ (BPRS)	X	X	X	X	X	X
8w	+ (PANSS)		X		X	X	
16w	- (BPRS)						X
12w	- (PANSS)		X				
6w	+ (BPRS)		X				
8w	- (scale?)				X		

Table 1 Continued

	Study	Country	DB	Pl	n (I/C)	Comparison
26	(Xin et al., 2001)	China?	N	N	64 (32/32)	CLZ + RIS vs. CLZ.
27	(Xu, 2006)	China	?	N	64 (32/32)	CLZ + SULP vs. CLZ
28	(Yue et al., 2004)	China?	N	N	46 (19/27)	CLZ + RIS vs. CLZ
29	(Zhang and Xu, 1989)	China	Y	?	37 (20/17)	CLZ + CPZ vs. CLZ
30	(Zhu and Deng, 2002)	China?	N	N	84 (42/42)	CLZ + PIP vs. CLZ
31	(Zhu et al., 1999)	China?	N	N	59 (29/30)	CLZ + SUL vs. CLZ
32	(Zou et al., 2003)	China?	N	N	61 (30/31)	CLZ + SUL vs. CLZ.
RCT's involving non-clozapine combinations						
33	(Barrett et al., 1957)	US	Y	Y	30 (10/10/10)	RES + CPZ vs RES RES + CPZ vs CPZ
34	(Chien and Cole, 1973)	US	N	N	46 (15/15/16)	CPZ+ FLU vs. CPZ CPZ + FLU vs. FLU
35	(Higashima et al., 2004)	Japan	N	N	19 (9/10)	HAL + LEV vs. HAL
36	(Kotler et al., 2004)	Israel	N	N	17 (9/8)	OLZ + SUL vs. OLZ
37	(Nishikawa et al., 1985)	Japan	Y	N	93 (47/24/22)	PIM + THI vs. PIM PIM + THI vs. THI
38	(Talbot, 1964)	US	Y	Y	77 (27/25/25)	CPZ + TRI vs. CPZ CPZ + TRI vs. TRI
39	(Yagi, 1976)	Japan	Y	Y	233 (116/117)	CPZ + PER vs. CPZ

Legend: AMISUL = amisulpride, ARI = aripiprazole, BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions scale, CLZ = clozapine, CPZ = chlorpromazine, DB = double blind, Dur. = trial duration, FLU = fluphenazine, GAF = Global Assessment of Functioning, HAL = haloperidol, HAM-D = Hamilton Depression Rating Scale, LEV = levomepromazine, MADRS = Montgomery Åsberg Depression Rating Scale, n (I/C) = total participants (number allocated to intervention arm / number allocated to control arm), N = no, OLZ = olanzapine, Outcome (+ / -): + = intervention significant superior, - = intervention not significant superior, PANSS = Positive and Negative Syndrome Scale, PER = perphenazine, Pl = placebo controlled, PIM = pimozide, PIP = pipothiazine, RCT = Randomized Controlled Trial, RES = reserpine, RIS = risperidone, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms, SER = sertindole, SUL = sulpiride, THI = thioridazine, TRI = trifluoperazine, Y = yes,? = unclear.

Dur.	Outcome (+/-)	Included in review by					
		Paton et al., 2007	Barbui et al. 2008	Taylor & Smith, 2009	Correll et al., 2009	Wang et al. 2010	Taylor ea 2011
12w	- (BPRS)		X				
8w	- (SANS)					X	
96w	- (PANSS)		X				
8w	- (BPRS?)				X		
24w	+ (BPRS)		X				
12w	- (BPRS)		X		X	X	
12w	- (BPRS)		X				
12w	- (scale?)				X		
4w	+ (scale?) - (scale?)				X		
8w	+ (agitation) - (pos/neg sympt (BPRS)				X		
8w	- (PANSS) + (HAM-D)				X		
52w	+ + (number of symptom free days, no scale)				X		
32w	+ + (no scale)				X		
17w	- (Keio Psychiatric Rating Scale for Schizophrenia, Keio Behavioral Rating Scale and general improvement rating)				X		

In table 2 we summarize characteristics and outcomes of the 6 systematic reviews included in this paper.

Table 2 Summary of 6 systematic reviews studying efficacy of antipsychotic combinations in schizophrenia

Study	n	N	Included Studies	Intervention vs. comparison	Outcome	Efficacy dichotomous outcome: RR (95% CI) *(study-defined inefficacy)*	Efficacy continuous outcome: SMD (95% CI) *(change on rating scale)*
(Barbui et al., 2009)	21	1480	(Un)blinded RCT's in clozapine treated schizophrenia	CLZ + any AP vs. CLZ	Dichotomous: Response (≥20 or ≥30% reduction on PANSS/BPRS) Continuous: score on PANSS/BPRS	Open RCT's: 0.64 (0.42 to 0.97) Double blind RCT's: 0.91 (0.75 to 1.11)	Open RCT's: -0.80 (-1.14 to -0.46) Double blind RCT's: -0.12 (-0.57 to 0.32)
(Correll et al., 2009)	19	1216	(Un)blinded RCT's in schizophrenia	Any AP (incl. CLZ) + any AP vs. any AP (incl. CLZ)	Dichotomous: Response (≥50% reduction on PANSS/ BPRS, "much better" on CGI)	0.76 (0.63 to 0.90)	
(Paton et al., 2007)	4	166	(Un)blinded RCT's in clozapine-treated schizophrenia	CLZ + any AP vs. CLZ	Dichotomous: Response (≥20% reduction on PANSS/BPRS)	Trial duration ≥ 10w: 0.22 (0.07 to 0.72)* Trial duration < 10w: 1.69 (0.76 to 3.70)	
(Taylor and Smith, 2009)	10	522	Blinded RCT's in clozapine-treated schizophrenia	CLZ + any AP vs. CLZ	Continuous: score on PANSS/BPRS		-0.180 (-0.356 to -0.004)
(Taylor et al., 2012)	14	734	Blinded RCT's in clozapine-treated schizophrenia	CLZ + any AP vs. CLZ	Continuous: score on PANSS/BPRS		Overall-0.239 (-0.452 to -0.026) Trial duration ≥ 10w-0.223 (-0.432 to -0.015) Trial duration < 10w-0.103 (-0.365 to 0.158)
(Wang et al., 2010)	4	221	(Un)blinded RCT's in schizophrenia and schizophrenia-like psychosis	Any AP (incl. CLZ) + sulpiride vs. any AP (incl. CLZ)	Dichotomous: Clinically important response in global state	Trial duration < 12w: 0.58 (0.3 to 1.09) Trial duration > 26w: 0.67 (0.42 to 1.08)	

Legend: AP = antipsychotic, BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impression scale, CI = confidence interval, CLZ = clozapine, n = number of studies, N = number of participants, PANSS = Positive And Negative Syndrome Scale, RCT = randomized controlled trial, RR = relative risk, SMD = standardized mean difference, * = Converted from efficacy to study-defined inefficacy by the authors

In 2009 Barbui et al. analysed all randomized controlled trials (irrespective of blindness and not necessarily placebo controlled) between 1966 and 2007 on efficacy of clozapine in combination with a second antipsychotic versus clozapine monotherapy in schizophrenic patients partially responsive to clozapine (Barbui et al., 2009). They included 21 randomized studies (6 double blind placebo-controlled and 15 open RCT's) with in total 1480 patients. Fifteen randomized trials were conducted in China, where diagnostic inclusion criteria were not based on DSM or ICD criteria. Efficacy was defined as change in group mean score on a rating scale and proportion of patients without response. Open studies significantly favoured combination strategies, while double blind studies did not. They concluded that the evidence base supporting clozapine combination strategies is weak, with modest to absent clinical benefit.

In the same year, a Cochrane systematic review was performed by Correll et al. (19 RCT's, including several studies in Chinese; 1216 patients) of studies combining a first generation antipsychotic (FGA) and a second generation antipsychotic (SGA) (including clozapine) in not necessarily treatment resistant schizophrenia (Correll et al., 2009). Primary outcome was 50% symptom reduction on PANSS/BPRS. They concluded that in certain clinical situations antipsychotic co-treatment might be superior to monotherapy. However, the database was subject to possible publication bias favouring combinations and too heterogeneous to derive firm clinical recommendations.

In 2007 Paton et al. conducted a meta-analysis of RCT's investigating clozapine augmentation with another antipsychotic drug in patients partially responding to clozapine (Paton et al., 2007). They included 4 studies with in total 166 patients. Response was defined as a reduction of 20% or more on BPRS/PANSS total scores, although clinical relevance of such reduction is modest. Analysis by study duration (>10 weeks) of RCT's accounted for heterogeneity in effect size, whereas analysis by drug did not. They concluded that in patients partially responsive to an adequate clozapine trial, augmentation with another antipsychotic drug in an individual clinical trial longer than 6 weeks might be useful.

Taylor & Smith performed an update of this study in 2009 with both new and unpublished trials, analysing 10 randomized placebo-controlled trials of at least 6 weeks augmenting clozapine with a second antipsychotic (Taylor and Smith, 2009). They found only weak evidence of therapeutic benefit with limited clinical significance and an association with study duration was not confirmed.

In 2012 Taylor et al. updated their 2009 meta-analysis of augmentation of clozapine with a second antipsychotic (Taylor et al., 2012). They found four new RCT's, resulting in 14 RCT's (all placebo controlled) including 734 patients. They conclude that augmentation of clozapine with a second antipsychotic is modestly beneficial and again no significant positive effect of treatment duration longer than 10 weeks.

A 2010 published Cochrane systematic review by Wang et al. studied the additive effect of sulpiride augmentation to any antipsychotic (including clozapine) for people with schizophrenia or schizophrenia-like psychosis (Wang et al., 2010). They identified four RCT's (three 8-12 weeks follow up, one 3 years follow up) including 221 patients. Three of these RCT's were included in the earlier mentioned and broader review of Barbui et al. (Barbui et al., 2009). The authors concluded that short-term (12 weeks) sulpiride plus clozapine is probably more effective than clozapine alone in producing clinical improvement in an unspecified subgroup of treatment resistant patients. However, the evidence was weak and prone to considerable publication bias in favour of positive studies.

Tolerability

In studies investigating tolerability of APP, associations with several adverse drug effects were found:

High-dosing and extrapyramidal side effects

We found no systematic reviews investigating a possible association of APP with high-dosing or extrapyramidal side effects. In several cohort studies APP is associated with high-dose antipsychotic drug prescribing, in both in- and outpatients (Barbui et al., 2006; Ranceva et al., 2010). In a case-control study of APP, high dosing is associated with increased risk on extrapyramidal side effects (Centorrino et al., 2004). In another case-control study, no difference in use of anticholinergics between monotherapy and polypharmacy groups was found, but this publication provides no information on prescribed doses (Ganesan et al., 2008). High dosing might also be associated with acceleration of frontal grey matter reduction (Weinmann and Aderhold, 2010).

Increased mortality

We found one systematic review investigating the influence of antipsychotics on mortality in schizophrenia (Weinmann et al., 2009). This review included 12 cohort studies comparing mortality in people with schizophrenia on antipsychotic medication versus people that did not use antipsychotics, not only on APP (n=4) but also on various doses of antipsychotic monotherapy (n=8). Due

to several methodological problems, they could not conduct statistical analyses necessary for a meta-analysis. The included four uncontrolled cohort studies on APP were inconclusive. In a large, in the same year published 11-year follow-up study including 66,881 patients with schizophrenia, overall mortality in patients on APP was not higher than in patients on antipsychotic monotherapy (Tiihonen et al., 2009).

Metabolic syndrome

We found no systematic reviews studying the risk of APP on development of metabolic syndrome. In a large Danish study with 10-year follow-up the rates of incident diabetes significantly increased with the number of combined antipsychotic drugs from 1.48 (95% CI 1.44 – 1.51) in patients prescribed 1 antipsychotic, 1.68 (95% CI 1.61 – 1.76) in case of 2 concomitant antipsychotics and up to 3.41 (95% CI 3.03 – 3.83) in patients on 5 or more antipsychotics (Kessing et al., 2010). In a cross-sectional study, patients on APP have higher rates of metabolic syndrome and lipid markers of insulin resistance, but APP was not independently associated with these abnormalities but rather was postulated to potentiate underlying risk factors (Correll et al., 2007). An association of APP with pre-metabolic syndrome (visceral fat obesity in combination with elevated blood glucose, lipid abnormalities or elevated blood pressure) was found even after correcting for patients' lifestyle characteristics, but not with metabolic syndrome (Misawa et al., 2011). These findings suggest that APP perhaps is a mediating rather than a direct factor for metabolic syndrome, but nevertheless might attribute to increased cardiovascular morbidity.

Cognitive dysfunction

We found no systematic reviews investigating APP in relation to cognitive dysfunction. In two cross-sectional studies APP is associated with decreased cognitive functioning (Chakos et al., 2006; Hori et al., 2006). This is probably due to excessive antipsychotic dosage and cumulative anticholinergic activity rather than number of antipsychotic drugs (Elie et al., 2010). A third study, however, found no association between APP or high-dosing and non-verbal cognitive functioning (Kontis et al., 2010).

Non-adherence

Complexity of medication regime is associated with non-adherence (Chen, 1991), suggesting that APP might increase the risk of non-adherence (Schorr et al., 2008). However, we did not find any clinical studies in patients receiving APP confirming this hypothesis.

Cost-effectiveness

We found no systematic reviews or controlled trials investigating cost-effectiveness of APP. A large (pharmaceutical industry funded) nonrandomized naturalistic prospective study concludes that APP adds substantial cost to treatment of schizophrenia (Zhu et al., 2008). These costs may be up to 3 times more per patient compared to monotherapy in case of combination of two SGA's (Stahl and Grady, 2006). In a cross-sectional observational study, APP is also associated with increased use of health care services (Baandrup et al., 2012). There is no evidence that these extra costs would be compensated by reduction of other health care costs like higher level of social functioning, less hospitalization or reduced duration of hospitalization (Centorrino et al., 2004; Clark et al., 2002; Janssen et al., 2004; Stahl and Grady, 2006).

Discussion

The translational research model as proposed by Honer et al. (Honer et al., 2009) stresses the importance of including basic science, knowledge on efficacy, tolerability as well as cost-effectiveness in the process of improving high-quality pharmacotherapy for patients with schizophrenia. It also provides a model that reveals gaps that need to be addressed before practicing APP as a high-quality pharmacotherapeutic strategy in psychotic disorders.

Our literature study reveals that APP is often based on neurobiological hypotheses that have minimal attention in pre-clinical or clinical research and lack empirical evidence. The dopamine hypothesis is the most investigated theoretical framework for APP, however it is insufficient especially in non-clozapine combinations since both antipsychotic agents compete with the same D_2-receptor. But also in APP involving clozapine the concept is insufficient since the antipsychotic with the weakest D_2 binding (clozapine) is replaced by the added antipsychotic that has stronger D_2 affinity (Taylor and Smith, 2009).

Efficacy of APP is limited to some evidence in augmenting patients (partially) resistant to clozapine, however with modest clinical benefit. Positive results are associated more with treatment duration of 10 or more weeks than with the added antipsychotic agent, especially in clozapine treated patients. However, partially due to complexity of the subject and the investigated population, studies are hampered by low patient numbers, large variety in duration of illness, mixing patients that received clozapine treatment and patients that did not, unclear criteria in case of

refractoriness, lack of adequate control for confounders (e.g. in time cumulating antipsychotic effect or pharmacokinetic interactions resulting in altered blood levels of the primary agent), short follow up periods, frequent absence of assessment scales evaluating effect and risk of publication bias, limiting definitive conclusions (Stern et al., 1997; Tranulis et al., 2008).

APP is associated with several serious risks such as high dosing, increased mortality, metabolic syndrome, cognitive impairment, and non-adherence; however, causality has not been demonstrated. Except for non-adherence, these adverse effects may as well be related to excessive dosing (or severity of the psychotic disorder itself) as to the number of prescribed antipsychotics APP brings up increased medication cost without evidence supporting cost-effectiveness.

According to the current available evidence, short term APP can be appropriate in a process of switching antipsychotics that may last up to 70 days in case of switching to some long-acting antipsychotics (see: www.switchingantipsychotics.eu). This switch needs to be completed, even if a patient recovers during the switch, in order to prevent getting trapped in cross-titration (Stahl, 1999). APP can also be appropriate as a trial in patients with severe psychotic symptoms not responding to adequate trials of successively two different antipsychotics and clozapine. These findings are in line with current recommendations in clinical guidelines (Lehman et al., 2004; National Institute for Clinical Excellence, 2009).

Reducing persistent APP to monotherapy without clinical deterioration has been successfully demonstrated in both in- and outpatient studies, although some patients relapsed (Chong et al., 2006; Essock et al., 2011; Suzuki et al., 2004). There is some evidence that intensive auditing and feedback from pharmacists may be effective in reducing inappropriate APP (Hazra et al., 2011; Weinmann et al., 2008), although clinicians' prescribing practices do not change easily (Howes et al., 2012). There are indications that persistent APP in inpatients might be a valid indicator to identify treatment problems and provides opportunities to enhance quality of treatment (Janssen et al., 2004).

A limitation is the small number of methodologically heterogeneous studies addressing antipsychotic polypharmacy that are included in the 6 reviews. Only one of these 6 reviews included non-clozapine combinations (Correll et al., 2009). More research is needed in the prevention of inappropriate persistent APP (including high-dosing) by addressing beliefs and attitudes of clinicians towards APP (Correll et al., 2011). There also is an urgent need for more evidence-based

guidance (e.g., more effective therapeutics) in patients with clozapine refractory psychotic symptoms that account for 25-30% or even more of patients suffering from schizophrenia and in which several somatic and pharmacotherapeutic strategies (including persistent APP) are frequently practiced by trial and error. We need to understand more about the characteristics of the subgroup of psychotic patients that appear to benefit from APP (including non-clozapine combinations) and relapses when revised to monotherapy versus the subgroup that does not relapse. Such research needs large double blind controlled trials with independent financial funding. However, randomised controlled trials may not be the most appropriate approach to address these issues because of the methodological problems mentioned above and limitations in external validity to real world clinical practice (Stahl, 2012). Naturalistic prospective study designs as well can provide opportunities to include larger numbers of patients and compare outcomes of different combination strategies (Miller and Craig, 2002). Routine outcome monitoring (ROM) can be a useful supportive tool to monitor systematically and thoroughly clinical and functional outcome in these studies.

Meanwhile, because of potential serious risks and modest clinical benefits, APP should be practiced with great caution (Langan and Shajahan, 2010). In clozapine refractory patients a trial with APP of sufficient duration (at least 10 weeks) with well-defined evaluation criteria (with use of rating scales integrated in ROM) can be a modest option that needs to be weighed against benefits and risks of other biological interventions in treatment resistant psychosis. If this trial proves ineffective, advice is to return to monotherapy with the primary agent.

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Chapter 4

The Additional Effect of Individualized Prescriber-Focused Feedback on General Guideline Instruction in Reducing Antipsychotic Polypharmacy in Inpatients

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Abstract

Purpose/Background: Antipsychotic polypharmacy (APP) is the concurrent use of more than one antipsychotic by a patient. Multiple antipsychotics are often prescribed although all relevant guidelines discourage this practice. These recommendations are based on a lack of evidence for effectiveness and an increased risk of serious adverse events with APP. Studies on the effects of educational interventions targeted at physicians have demonstrated inconclusive results. Moreover, it is unclear how individualized these interventions need to be. In this study we aimed to assess the effect of a general intervention and the additional impact of an individualized, prescriber-focused intervention on guidelines adherence, i.e., the prescription of APP.

Methods/Procedures: We conducted a 36-month two-step serial intervention study with 4 stages of 9 months each (baseline, general intervention, addition of an individualized intervention, and follow up) including all 20 inpatient units of one regional mental health organization. The primary outcome was the proportion of patients with regular prescriptions for APP ≥ 30 consecutive days across all patients with a prescription of at least one antipsychotic. The secondary outcome was the proportion of patient days on APP over the total number of patient days on at least one antipsychotic.

Findings/Results: The general intervention was ineffective on both outcome measures. Addition of an individualized intervention decreased the proportion of patients with prescriptions for episodes of persistent APP significantly by 49.6%. The proportion of patient days on APP significantly decreased by 35.4%.

Implications/Conclusions: In contrast to a general intervention, the addition of an individualized intervention was effective in improving adherence to guidelines with respect to APP prescription in inpatients.

Keywords: antipsychotic polypharmacy, guideline adherence, antipsychotics, reduction, general intervention, individualized intervention.

Introduction

Antipsychotic polypharmacy (APP) is the concurrent use of ≥ 2 different antipsychotic (AP) agents by a patient and is reported worldwide in approximately 20% of patients with a psychotic disorder. Over the last decades APP prescriptions have increased in several western countries (Gallego et al., 2012). The most prevalent reason for clinicians to prescribe APP is to treat persistent psychotic symptoms (Sernyak and Rosenheck, 2004). Adjunctive antipsychotics are also prescribed to manage side effects of the primary antipsychotic agent (Shim et al., 2007; Fleischhacker et al., 2010). Finally, APP may be the result of an unfinished cross-titration switch of antipsychotics (Stahl, 1999).

In contrast to its widespread use, robust scientific evidence supporting efficacy of APP is lacking and it is associated with enhanced risk of adverse or unintended effects, including increased risk of high dose prescription, extrapyramidal side effects, drug interactions and metabolic syndrome, decreased cognitive functioning and medication compliance, and extra medication costs (Lochmann van Bennekom et al., 2013; Fleischhacker and Uchida, 2014). Guidelines therefore advocate antipsychotic monotherapy and advice to limit use of APP to cross-titration during switch of antipsychotics, and as an option in clozapine resistant patients (Moore et al., 2007; Kuipers et al., 2014; van Alphen et al., 2012).

This contrast between guideline recommendations and routine clinical practice is well known and underpins the need for evidence-based educative strategies to improve adherence to guidelines (Bauer, 2002; Bero et al., 1998). These strategies can vary from relatively inexpensive general educational interventions to more expensive individualized interventions. Studies investigating the effects of general interventions (one-way dissemination of knowledge) and individualized prescriber-focused interventions (active, prescriber directed forms of communication) in reducing APP showed inconclusive results (Mace and Taylor, 2015; Tani et al., 2013; Weinmann et al., 2008). A general intervention was superior to usual care in all 3 uncontrolled open label studies, but in none of the 3 randomized controlled trials. An individualized intervention was effective in reducing APP in all 11 uncontrolled open label studies but in only 1 of the 3 randomized controlled trials. Given the considerable higher cost of individualized interventions, it is important to know the additional effect of an individualized intervention over a general intervention. This can be investigated by testing both types of interventions in a two-step serial intervention design. We found 2 studies applying this design, demonstrating efficacy of a general intervention and additional efficacy of a prescriber-focused

intervention (Goren et al., 2010; Finnerty et al., 2011). However, methodological issues including inclusion criteria (only including patients at discharge in one study) and the definition of APP (concomitant use of ≥ 3 antipsychotics in the other study) limit their generalizability. Therefore, further research on the effects of general and additional individualized prescriber-focused interventions on adherence to guidelines in prescribing antipsychotics with respect to APP is warranted. The aim of the present study was to assess the effect of a general intervention and the additional effect of an individualized prescriber-focused intervention on antipsychotic prescriptions.

Methods

Study design and setting

We conducted a two-step serial intervention study from October 1st 2008 until August 1st 2012 in adult inpatients in a regional mental health hospital in the Netherlands with 324 beds in 20 wards, i.e., 3 adult admission units, 12 adult rehabilitation/long-stay units, 1 adolescent unit for both admission and rehabilitation, and 4 elderly units including 1 admission and 3 rehabilitation units. There was no control group that was not exposed to the interventions. The study period lasted 1080 days and included 4 stages of each 270 days:

- Baseline (stage 1),
- General intervention (stage 2),
- General + individualized intervention (stage 3) and
- Follow up (stage 4).

Due to technical issues, initiation of stage 3 was delayed by 5 months (150 days). During that delay the general intervention was continued, but we did not include the data of this period in our analyses.

Subjects

Subjects were all 11 psychiatrists and 5 residents of the hospital's adult inpatient units. Besides these 16 physicians, the institution has 28 physicians (21 senior staff members, 7 residents) who could incidentally become involved in the study during evening, night, or weekend shifts, resulting in 44 potentially involved physicians. Psychiatrists had clinical experience varying from 2 up to 30 years. Early career psychiatrists more frequently worked at admission wards. As required in the Netherlands, all psychiatrists had a board certification that requires 20 hours of

continuous medical education (CME) per year which needs to be renewed every 5 years to maintain registration as a medical specialist. During the study there were no changes in psychiatrists. Residents changed according to their trainee-program every 6 - 12 months.

Outcome measures

- Primary outcome: the proportion of patients meeting criteria for APP ≥ 30 days over all patients on ≥ 1 AP.
- Secondary outcome: the proportion of patient days on APP over all patient days on ≥ 1 AP.

Data collection

From the hospital's pharmacy we collected start/stop dates of all antipsychotic prescriptions (including low dose quetiapine, levomepromazine and pipamperone) from all adult (≥ 18 years) inpatients irrespective of diagnosis. Since APP is associated with younger age and longer duration of hospitalization (Suokas et al., 2013; Ganguly et al., 2004), data on age and clinical setting (admission versus rehabilitation/long-stay units) were collected as potential influencing factors. Because we aimed to investigate change in guideline adherence as reflected in APP prescriptions, we collected no data on gender, socio-demographic backgrounds or on (beneficial or harmful) change in psychopathology of the patients involved. Although 'as-needed' (PRN) prescriptions of antipsychotics are a potentially major contributor to APP (Paton et al., 2008), we excluded these because we could not determine if PRN medication was actually administered.

In each stage we registered the number of patients on ≥ 1 AP and the number of patient days on ≥ 1 AP, patient days on APP, and any intercurrent patient days without AP prescription. We determined patients with episodes of persistent APP in each stage. To exclude appropriate APP during crossover switch of antipsychotics, which can usually be limited to 4 weeks in oral antipsychotics, we studied episodes of APP ≥ 30 consecutive days. Since APP can in some cases be appropriate up to 10-12 weeks, e.g., when switching to aripiprazole or to long-acting injectable antipsychotics (http://wiki.psychiatrienet.nl/index.php/SwitchAntipsychotics, accessed: March 13, 2020), we also studied data for episodes of APP ≥ 60 and ≥ 90 days. If an episode continued over 2 stages, we assigned it to the stage that covered ≥ 50% of the APP days of that episode. If a patient had more than one episode of APP in a stage, we only counted the first one as a new event. If a patient had episodes of APP in multiple stages, we counted only the first episode in each stage. Episodes of APP in patients treated in admission units were registered as

'admission'; episodes in patients treated in rehabilitation/long-stay units were registered as 'rehabilitation'. Episodes of APP in patients transferred from an admission to a rehabilitation/long-stay unit were also registered as 'rehabilitation'.

Study stages and interventions

Baseline (stage 1)

In this stage without any intervention, baseline data on prescriptions of antipsychotics was collected.

General intervention (stage 2)

In this stage we started sending 3-monthly e-mails to all physicians giving information about the project, and providing general information on epidemiology, efficacy and safety of APP. Based on the current Dutch guidelines on treatment of patients with schizophrenia, we recommended to practice APP only during crossover switching of antipsychotics, or as a trial in patients refractory to adequate trials with two different antipsychotics and clozapine (van Alphen et al., 2012). An English translation of this mail text is provided in the Supplemental Material (text mail 1).

General + individualized prescriber-focused intervention (stage 3)

At the beginning of this stage, all physicians once more were informed by e-mail about the project including background information on APP, and the start of the additional individualized intervention. An English translation of this mail is provided in the Supplemental Material (text mail 2). At both locations of the institute we scheduled 60-minutes lasting interactive lunch seminars for all (para) medical staff, providing extensive scientific information on safety and efficacy of APP, the treatment algorithm according to the current Dutch guidelines, and their recommendations with regard to APP.

In addition to the ongoing 3-monthly general guideline instruction e-mails, an individualized e-mail was sent by the hospital's pharmacy on behalf the first author to the prescribing physician for any patient on existing APP and immediately after each new prescription resulting in APP, explaining the reason of the mail, and providing the name and date of birth of the patient involved. We referred to the examples of appropriate APP and the questionable application in sedation (sleep disorders and agitation) and requested the prescriber to report the reason of the APP to the first author by selecting one out of four options (switch of antipsychotics, treatment refractoriness, sedation, or other reasons). An English translation of this mail is provided in the Supplemental Material (text mail 3). If the physician did

not reply to this request on indication within one week, we sent reminder e-mails every week. The physician was also offered the opportunity for telephone or e-mail consultation about the APP.

Follow up (stage 4)

During follow up all interventions were aborted, while the data collection of prescribed antipsychotics continued.

Statistical analyses

Primary outcome

Since each patient could contribute data in multiple stages, we applied a generalized estimating equation (GEE) logistic regression model for dichotomous nominal data with patients yes or no on APP ≥ 30 days as dependent variable and study stage, age (clusters of 18-40, 40-65, and ≥ 65 years) and setting (admission versus rehabilitation unit) as independent variables. The GEE logistic regression model provides a nonparametric way to handle repeated measurements, taking into account an expected correlation of the measurements within each individual, and estimates the population average effects. We applied type 3 analyses of effects to determine an overall effect on APP prescriptions. If there was a statistically significant effect, we calculated estimated probabilities (odds ratios [OR] and their 95% confidence intervals [CI]) of APP ≥ 30 days per stage, separately for age and setting. We tested for stage x setting and stage x age interaction. We performed identical analyses for APP ≥ 60 and ≥ 90 days.

Secondary outcome

We determined the proportion of patient days on APP. To assess differences between stages we applied a negative binomial GEE regression model for continuous data with number of patient days on APP as the dependent variable and study stage, age, and setting as independent nominal variables. The negative binomial model estimates the rate of events (i.e., the proportion APP days) per time period as a function of the explanatory variables (i.e., study stage, age and setting). The relation between event rate and explanatory variables is expressed in incidence rate ratios (IRR). A larger IRR indicates a larger proportion of APP days.

We applied type 3 analyses of effects to determine an overall effect. If there was a statistically significant effect, we calculated estimated probabilities (IRR and their 95% CI) of patient days on APP per stage, separately for age and setting. Again, we checked for stage x setting and stage x age interaction.

A two-tailed α-level of.05 for significance was adopted. Analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Medical ethical issues

Data about prescriptions and the prescribing physician were collected anonymously, except in stage 3, where the prescribing physician and the patient involved were disclosed to only the first author. The study was conducted in accordance with the institute's internal ethical guidelines, reported to the institute's patient council and was approved by the board of the institute, who permitted that no informed consent of the participating physicians was needed. Doctors remained free to choose which antipsychotic to prescribe, including APP, without any professional or personal consequences of this choice.

Results

We included 1880 episodes with prescriptions of ≥ 1 AP in 970 unique patients. From these 970 patients, 521 (53.7%) were included in one stage only, 184 (19.0%) in 2 stages, 69 (7.1%) in 3 stages and 196 patients (20.2%) were included in all 4 study stages. Table 1 presents the distribution of patients by age and clinical setting per study stage.

Table 1 Patients per stage by age and setting

	Stage 1 (n=439)	**Stage 2 (n=464**	**Stage 3 (n=484)**	**Stage 4 (n=493)**
Age in years	**n (%)**	**n (%)**	**n (%)**	**n (%)**
18 – 40	146 (33.3)	166 (35.8)	176 (36.4)	184 (37.3)
40 – 65	185 (42.1)	204 (44.0)	215 (44.4)	217 (44.0)
≥ 65	108 (24.6)	94 (20.2)	93 (19.2)	92 (18.7)
Setting	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Admission	128 (29.1)	142 (30.6)	163 (33.7)	182 (36.9)
Rehabilitation	311 (70.9)	322 (69.4)	321 (66.3)	311 (63.1)

The distribution of patients exposed to AP prescriptions per study stage, including the prescribed combinations of first- and second-generation AP's and clozapine, is presented in table 2. Combinations of two SGA's were most frequent across all stages (32-40%), followed by combinations of two FGA's (19-30%) and combinations of clozapine with an FGA or SGA. Combinations of an FGA with an SGA were the least common (16-18%). Long-acting injectable antipsychotics (LAI's) were involved in approximately 5.5% of all antipsychotic prescriptions.

Table 2 Observed values for patients on ≥ 1 AP, patients on APP ≥ 30 days, patient days on ≥ 1 AP, patient days on APP, their proportions over all patients on ≥ 1 AP resp. patient days on ≥ 1 AP, and APP combinations per study stage.

	Stage 1	Stage 2	Stage 3	Stage 4
Patients on ≥ 1 AP	439	464	484	493
Patients on APP ≥ 30 days.	107	127	67	71
Proportion APP (patients on APP ≥ 30 days/patients on ≥ 1 AP)	.244	.274	.138	.144
Patient days on ≥ 1 AP	61,647	62,062	62,616	61,415
Patient days on APP	34,922	40,634	26,517	27,458
Proportion patient days on APP (patient days on APP/patient days on ≥ 1 AP)	.566	.655	.423	.447
	32	17	16	22
APP combinations (N; %) at the end of stage:	(30.5%)	(25.0%)	(19.0%)	(27.2%)
FGA + FGA	17	12	14	15
FGA + SGA	(16.2%)	(17.6%)	(16.7%)	(18.5%)
SGA + SGA	42	24	35	26
Clozapine + any AP	(40.0%)	(35.3%)	(41.7%)	(32.1%)
	14	15	19	18
	(13.3%)	(22.1%)	(22.6%)	(22.2%)

Abbreviations: AP = antipsychotic, APP = antipsychotic polypharmacy**,** FGA = first-generation antipsychotic, SGA = second-generation antipsychotic

Patients receiving APP ≥ 30 days

The observed proportions of APP ≥ 30 days per stage, broken down by age and setting, are shown in figure 1. The overall proportion of APP ≥ 30 days was 3 times higher in patients hospitalized in rehabilitation vs. admission wards (OR 3.00, 95% CI 2.19 - 4.10, *P* <.0001) and almost 2 times higher in younger vs. older patients (OR 1.92, 95% CI 1.34 - 2.75, *P* =.0004). There was a clear overall intervention effect (*P* <.0001). In stage 2 (general intervention) we found no significant change in the proportion of patients exposed to APP ≥ 30 days (stage 2 vs. 1: OR 1.17, 95% CI 0.86 - 1.59, *P* = 0.32). In stage 3 (general + individualized intervention) there was a marked, significant decrease (stage 3 vs. 2: OR 0.42, 95% CI 0.30 - 0.59, *P* <.0001) (see Supplemental Material, table 1 for the regression model). The estimated probabilities of APP ≥ 30 days decreased in stage 3 in both clinical settings and in all 3 clusters of age (see Supplemental Material, figure 1). Besides study stage, the overall tests showed that both setting (*P* <.0001) and age (*P* =.0009) were significant predictors for episodes of APP. There was no stage x setting (*P* =.41) and no stage x age interaction (*P* =.53).

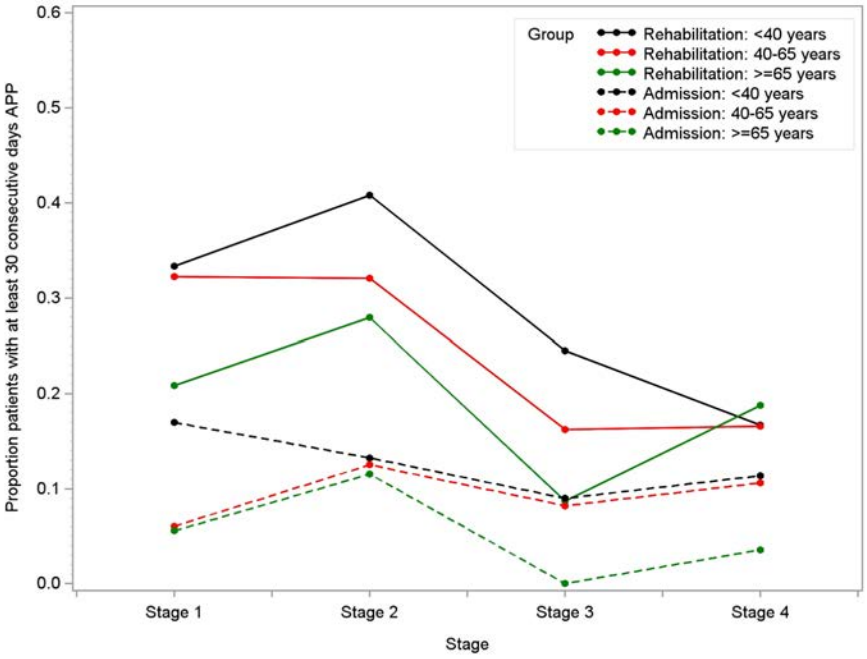

Figure 1 Observed proportions of patients on APP ≥ 30 days per stage, broken down by setting and age. Abbreviation: APP = antipsychotic polypharmacy

Analyses of episodes of APP ≥ 60 and ≥ 90 days revealed similar patterns with lower proportions of episodes and patient days on APP (data on request available from the first author).

Patient days on APP

The observed proportions of patient days on APP per stage, broken down by age and setting, are represented in figure 2. There was a small significant increase in the estimated probability of patient days on APP in stage 2 (stage 2 vs.1: IRR 1.12, 95% CI 1.03-1.22, *P* = 0.0092). In stage 3 we found a significant and clinically relevant decrease (stage 3 vs. 2: IRR 0.67, 95% CI 0.59 - 0.76, *P* <.0001) (see Supplemental Material, table 2 for the regression model). Besides study stage, both setting (*P* <.0001) and age (*P* =.0001) were significant predictors for patient days on APP. There was no stage x setting (*P* =.29) and no stage x age interaction (*P* =.17). The estimated probability of patient days on APP was higher in patients hospitalized in rehabilitation vs. admission wards (IRR 1.96, 95% CI 1.69- 2.29, *P* <.0001) and in younger vs. older patients (IRR 1.51, 95% CI 1.25 - 1.83, *P* =.0006). The estimated probabilities of patient days on APP decreased in stage 3 in both clinical settings and in all 3 clusters of age (see Supplemental Material, figure 2).

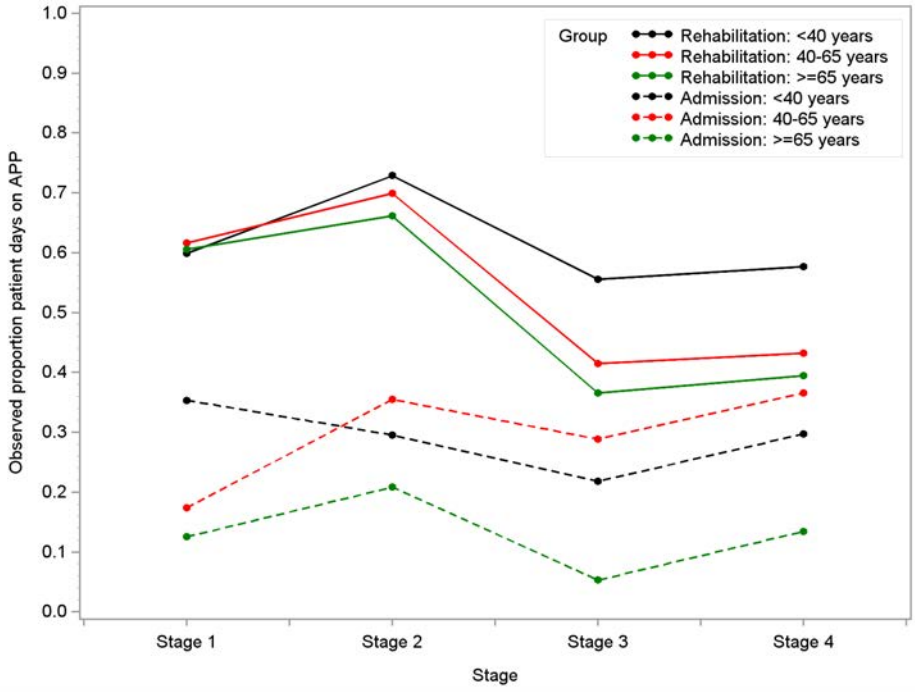

Figure 2 Observed proportions of patient days on APP per stage, broken down by setting and age.[a]

[a] Proportion APP = patient days on APP divided by all patient days on ≥ 1 AP.
Abbreviation: APP = antipsychotic polypharmacy.

Discussion

The aim of the present study was to investigate the effect of a general intervention and the additional effect of an individualized intervention on guideline adherence, i.e., the prescription of APP. With regard to the primary outcome, we found on average 24.4% prescriptions of persistent APP ≥ 30 days at baseline, that did not significantly change during the general intervention. Addition of the individualized intervention reduced APP episodes significantly to 13.8% (relative reduction: 49.6%). Episodes of APP ≥ 60 resp. ≥ 90 days showed similar patterns. Regarding the secondary outcome, we found 56.6% patient days on APP at baseline that slightly, although significantly, increased to 65.5% (relative increase: 15.7%) during the general intervention, but significantly and clinically relevant decreased to 42.3% (relative reduction: 35.4%) during the individualized intervention. Prescription of APP was clearly different between the two clinical settings (rehabilitation units > admission wards) and between the groups of age (youngest patients > oldest

patients), but the effect of the individualized intervention was independent of setting and age.

With respect to efficacy of the general intervention, our results are inconsistent with two previous studies that also applied a two-step serial intervention, but similar regarding the additional efficacy of an individualized intervention. The first is an inpatient study by Gören et al., who applied a 9-month general educational program followed by a 10-month individual audit feedback program (Goren et al., 2010). They found 64% reduction of APP after delivery of the general program and a further 56% reduction after addition of individual audit feedback. The more favorable outcome of the general intervention may be explained by the inclusion of a different group of patients, i.e., only patients at discharge, that may represent a population with less severe psychopathology in which medication reduction is easier to achieve compared to a more severely ill general clinical population. The second is a study by Finnerty et al., who investigated reduction of APP in a 5 years 3-stage study design (Finnerty et al., 2011). The 4-months first general intervention stage consisted of implementation of a web-based decision system that supports clinical guideline implementation and the need for approval for any third antipsychotic prescribed. The 20-month second individualized intervention stage consisted of additional quarterly patient-specific feedback. At follow-up (36 months), only the decision support system was available. They found a 43% reduction of APP during the general intervention, and an additional 60% reduction in the individualized intervention. Efficacy of the general intervention in this study may be explained by the more restrictive definition of APP (i.e., ≥ 3 antipsychotics simultaneously for more than 60 days), and the need for approval, making it a more personalized intervention.

Strengths of our study are the thorough data collection including all prescriptions, the inclusion of a mixed clinical sample of patients who were both acute as well as admitted longer-term, and the common definition of APP (i.e., two or more antipsychotics). Our findings need to be considered in the light of some limitations. First, as a consequence of the design of the study involving the entire hospital, there was no parallel control condition without any intervention to correct for any other potential influencing factors. Second, we have no information about patients' gender, socio-demographic backgrounds and psychopathology (including violent behavior), which are known factors that also impact (short and long term) APP (Biancosino et al., 2005; Kadra et al., 2016). Although these factors are unlikely to confound our results since they can be assumed (relatively) stable across stages, it leaves questions as to whether patients have improved, remained stable

or deteriorated. Third, we did not collect detailed information on prescribers' backgrounds (e.g., being an attending psychiatrist, years of clinical practice) that are also known to influence prescribing habits (Correll et al., 2011). However, as the psychiatric staff remained unchanged in the course of the study, this also can be considered a relatively stable factor, not likely to affect study outcome. Finally, the initiation of stage 3 was delayed by 5 months, however, it is unlikely that this influenced the results of this study, since a prolonged exposure to the general intervention would rather cause an increase than a decrease of the effect in stage 2 and is unlikely to explain a better outcome in stage 3.

Despite existing guidelines, APP is a widespread treatment strategy (Constantine et al., 2015) that is difficult to change (Owen et al., 2008; Thompson et al., 2008; Baandrup et al., 2010). Psychiatrist's skepticism towards the use of algorithms, nurses' requests for more drugs, and the patient's clinical condition may underlie the persistence of this practice (Ito et al., 2005). Yet, as demonstrated in this study, a program of individualized feedback, in contrast to a general intervention, may substantially increase adherence to guidelines and reduce APP in acute and chronically ill inpatients. Increasingly, electronic prescription systems are available that can give an alert to the physician when APP is prescribed. The extent to which these automated systems can replace this individualized feedback is an important question that requires further research.

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Supplemental Material

The Additional Effect of Individualized Prescriber-Focused Feedback on General Guideline Instruction in Reducing Antipsychotic Polypharmacy in Inpatients

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List of Supplemental Material

1. Supplemental Table 1: GEE Logistic regression model estimating the probability of APP ≥ 30 days as a function of stage, age, and setting.
2. Supplemental Table 2: GEE negative binomial regression model estimating the proportion of patient days on APP as a function of stage, age and setting.
3. Supplemental Figure 1: Estimated probabilities of persistent APP ≥ 30 days
4. Supplemental Figure 2: Estimated probabilities of patient days on APP per stage
5. Supplemental Text mail 1: text start general intervention (stage 2) (translated)
6. Supplemental Text mail 2: text start individualized intervention (stage 3) (translated)
7. Supplemental Text mail 3: text to prescriber when initiating APP (stage 3) (translated)

Supplemental Table 1: GEE Logistic regression model estimating the probability of APP ≥ 30 days as a function of stage, age, and setting

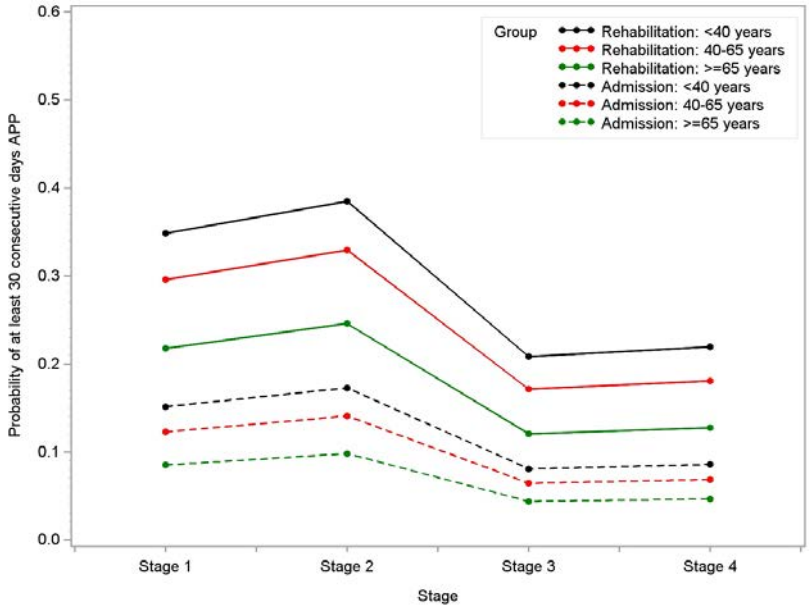
Variables	Comparison	Odds Ratio	95% Confidence Limits		P-value Chi-square	P-value Type III test
Stage						**<0.0001**
	Stage 2 vs Stage 1	1.1700	0.8586	1.5945	0.3200	
	Stage 3 vs Stage 1	0.4921	0.3522	0.6875	<.0001	
	Stage 4 vs Stage 1	0.5258	0.3759	0.7355	0.0002	
	Stage 3 vs Stage 2	0.4206	0.3015	0.5866	<.0001	
	Stage 4 vs Stage 2	0.4494	0.3266	0.6184	<.0001	
	Stage 4 vs Stage 3	1.0685	0.7477	1.5269	0.7161	
Age						**0.0009**
	Age 18-40 vs 40-65	1.2738	0.9589	1.6920	0.0948	
	Age 18-40 vs ≥ 65	1.9194	1.3417	2.7460	0.0004	
	Age 40-65 vs≥ 65	1.5069	1.0765	2.1094	0.0169	
Setting						**<0.0001**
	Rehabilitation vs. admission	2.9951	2.1895	4.0972	<.0001	

Abbreviations: GEE = generalized estimating equation, APP = antipsychotic polypharmacy

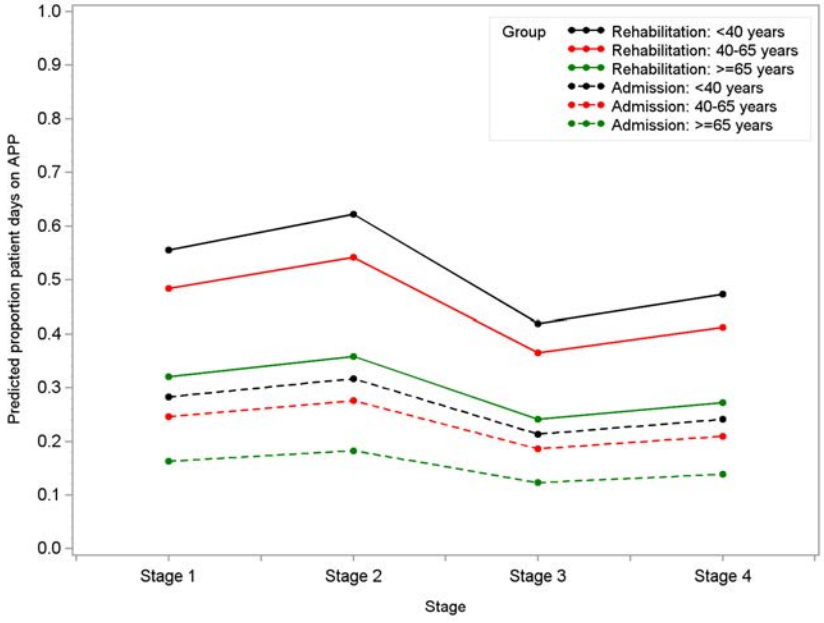
Supplemental table 2: GEE negative binomial regression modelestimating the proportion of patient days on APP as a function of stage, age, and setting

Variables	Comparison	Rate Ratio	95% Confidence Limits		P-value Chi-square	P-value Type III test
Stage						**<0.0001**
	Stage 2 vs Stage 1	1.1207	1.0286	1.2211	0.0092	
	Stage 3 vs Stage 1	0.7548	0.6549	0.8699	0.0001	
	Stage 4 vs Stage 1	0.8515	0.7378	0.9827	0.0279	
	Stage 3 vs Stage 2	0.6735	0.5945	0.7630	<0.0001	
	Stage 4 vs Stage 2	0.7598	0.6694	0.8623	<0.0001	
	Stage 4 vs Stage 3	1.1281	1.0058	1.2653	0.0396	
Age						**<0.0001**
	Age 18-40 vs 40-65	0.8709	0.7481	1.0138	0.0746	
	Age 18-40 vs ≥ 65	1.5118	1.2523	1.8251	<0.0001	
	Age 40-65 vs≥ 65	1.7359	1.4351	2.0998	<0.0001	
Setting						**<0.0001**
	Rehabilitation vs. admission	1.9645	1.6867	2.2880	<0.0001	

Abbreviations: GEE = generalized estimating equation, APP = antipsychotic polypharmacy



Supplemental figure 1: Estimated probabilities of persistent APP ≥ 30 days
Abbreviation: APP = antipsychotic polypharmacy



Supplemental figure 2: Estimated probabilities of patient days on APP per stage
Abbreviation: APP = antipsychotic polypharmacy

Supplemental text mail 1: text at start general intervention (stage 2) (translated)

To: all doctors of Nijmegen Mental Health Care

Nijmegen, July 2009

Dear Colleague,

I am currently conducting a study on antipsychotic polypharmacy (APP) in psychotic disorders. APP is the co-administration of 2 or more antipsychotics to the same patient. Prevalence of APP in Western European countries is 30-40%. Short-term co-administration of 2 antipsychotics may be necessary when switching antipsychotics. Efficacy of long-term APP has not been demonstrated, while this strategy entails risks, such as inadequate dosing, increased side effects and medication non-adherence.It is recommended that AP should be used in patients who do not or insufficiently respond to adequate treatment trials with two different antipsychotics followed by clozapine, and that the combination should only be continued if the patient has clearly improved. Our hope is to avoid unnecessary combinations of antipsychotics.I will remind you of this guideline by means of 3-monthly emails in the next 18 months (until January 2011) and monitor the effect of this alert on the prevalence of AP as a part of this study. I will report the findings of the study in due course.

Sincerely,
Marc Lochmann van Bennekom, psychiatrist

Supplemental text mail 2: text at start individualized intervention (stage 3) (translated)

To: all doctors of Nijmegen Mental Health Care

Nijmegen, April 2010

Dear Colleague,

As may be known from earlier emails, I am currently conducting a study into antipsychotic polypharmacy (APP) in psychotic disorders. APP is the co-administration of 2 or more antipsychotics to the same patient. Prevalence of APP in Western European countries is 30-40%. Short-term co-administration of 2 antipsychotics may be necessary when switching antipsychotics. Efficacy of long-term APP has not been demonstrated, while this strategy entails risks, such as inadequate dosing, increased side effects and medication non-adherence.It is recommended that AP should be used in patients who do not or insufficiently respond to adequate treatment trials with two different antipsychotics followed by clozapine, and that the combination should only be continued if the patient has improved. Our hope is to avoid unnecessary combinations of antipsychotics.

Since July 2009, I have reminded you of this through 3-monthly emails, and I will continue to do so until January 2011. You have recently received the most recent email (or will receive it shortly).

In addition, from April I will start with more intensive and more tailored interventions:

1. *In the appendix you will find the Dutch Multidisciplinary Guidelines on Treatment of Schizophrenia (where on p.164 there is a paragraph about combining antipsychotics), expecting that it can guide you in your choices practicing evidence-based (pharmaco)therapy in patients with a psychotic disorder.*

2. *On Tuesday April 6 from 12.30-13.30 (location Nijmeegsebaan, group room) and Tuesday April 13 from 12.30-13.30 (location Aurora, meeting room 2nd floor) I will give a lecture about antipsychotic polypharmacy, where you are all invited to.*

3. *From April 2010 to January 2011, the hospital's pharmacy ZALV will notify prescribers by mail if two (or more) antipsychotics are prescribed simultaneously*

for 30 days or more, so that you can re-evaluate this prescription policy on its necessity. The pharmacy will send a copy to me as part of the investigation.

4. *After 60 or more days of antipsychotic polypharmacy, I will contact you for consultation on the APP, inform about the reasons and I will think with you about possible alternatives. Obviously, as a prescriber, you will continue to make your own pharmacotherapeutic decisions and remain responsible for the pharmacotherapy.*

5. *Finally, you can send me your questions about antipsychotic polypharmacy by e-mail. In principle, I will answer these (if necessary after consultation with ZALV) within 5 working days, with the exception of the May holidays (30-4-10 to 16-5-10) and the summer holidays (31-7-10 to 22-8-10).*

Kind regards,
Marc Lochmann van Bennekom, psychiatrist

Supplemental text mail 3: text to prescriber when initiating APP (stage 3) (translated)

Dear Colleague,

The daily medication monitoring by the hospital's pharmacy ZALV shows that you have started prescribing 2 antipsychotics simultaneously. You receive this email alert from ZALV in the context of my study into reducing unnecessary antipsychotic polypharmacy (APP), about which I have informed all GGz Nijmegen doctors last July. In this context, I would suggest the following recommendations:

1. *Short-term APP (usually < 30 days) may be necessary while switching antipsychotics.*
2. *Addition of a 2nd, often low-dose sedative antipsychotic (including levomepromazine) is sometimes used temporarily in agitation or sleep disorders. This strategy is subject of discussion and is not recommended in current guidelines.*
3. *It is recommended to use long-term APP (> 30 days) only in patients who do not or insufficiently respond to adequate treatment trials with two different antipsychotics followed by clozapine, and that the combination should only be continued if the patient has improved.*

REQUEST

In the context of this research, I would also like to know the indication for which you prescribe two antipsychotics at the following email address mlochmannvanbennekom@ggznijmegen.nl:

1. Switching antipsychotics
2. Agitation / sleep disorder
3. Treatment resistant symptoms
4. Other reason, namely:

I hope I have been of service to you with this advice and look forward to your response.I am happy to be available for consultation.

Marc Lochmann van Bennekom, psychiatrist

Patient's name:
Date of birth:
Unit:
Antipsychotics:

Chapter 5

Antipsychotic polypharmacy in time course: evidence for a cross-titration trap

Marc W.H. Lochmann van Bennekom, Harm J. Gijsman, Joanna IntHout, and Robbert Jan Verkes

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Abstract

Purpose/Background: Antipsychotic polypharmacy (APP) is controversial yet applied in 20% of patients with psychotic disorders. We investigated indications for initiating and continuing APP, including the contribution of unfinished cross-titrations.

Methods/Procedures: This 2-month study was part of a prospective study to reduce inappropriate APP in inpatients. With each new prescription resulting in APP, we asked the prescriber for the indication (e.g., switching antipsychotics, sedation for agitation/sleep disorders, treatment refractoriness, other), and repeated this at 30 and 60 days. Secondary outcome was unfinished cross-titration at 60 days.

Findings/Results: In a consecutive cohort of 55 patients, 80% diagnosed with schizophrenia, switching antipsychotics was the primary initial indication for APP in 31/55 patients (56%), followed by sedation in 12/55 patients (22%), and treatment refractoriness in 10/55 patients (18%). Overall, APP was discontinued after 30 days in 25/55 patients (45%) and after 60 days in 28/55 patients (51%). At 60 days, APP initiated for switching antipsychotics was ongoing in 9/31 patients (29%), APP initiated for sedation was ongoing in 8/12 patients (66%), and APP initiated for refractoriness was ongoing in 9/10 patients (90%). The initial indication for APP was maintained at 60 days in 21/27 patients (78%). Unfinished cross-titration occurred in 9/31 patients (29%) with APP initiated for switching antipsychotics.

Implications/Conclusions: APP was initiated primarily because of cross-titration switching of antipsychotics. The reason for APP was a mostly consistently maintained over time, particularly when initiated for treatment refractoriness. Of all patients with APP initiated to switch antipsychotics, 29% ended in unfinished cross-titration.

Introduction

Although in most patients suffering from a psychotic disorder treatment is started with a single antipsychotic, worldwide approximately 20% of patients end up with antipsychotic polypharmacy (APP), here defined as the prescription of two or more antipsychotic agents simultaneously (Gallego et al., 2012). Intended short-term use of APP is often in a process of cross-titration switching of antipsychotics, but may persist if a patient improves in the course of this trajectory and the clinician does not taper the primary antipsychotic. In this situation, the treatment becomes "stuck" in cross-titration, sometimes referred to as the cross-titration trap (Stahl, 1999). There are various reasons for persistent APP (Correll et al., 2011; Ajayi and Arora, 2023; James et al., 2017; Chang and Kim, 2014; Kishimoto et al., 2013), but according to the literature the main reason is to treat refractory psychotic symptoms (Sernyak and Rosenheck, 2004; Correll and Gallego, 2012; Tapp et al., 2003), with the assumption that combining two antipsychotics with different receptor binding profiles is more effective (Guinart and Correll, 2020). APP is also prescribed for sedation, in order to treat sleep disorders (Stummer et al., 2018), or to treat agitation or violence in patients with psychotic disorders (Haw and Stubbs, 2003). Incidentally, combinations of antipsychotics are also prescribed to manage side effects of the primary antipsychotic agent (Shim et al., 2007; Fleischhacker et al., 2010). Despite its widespread use, the scientific evidence for the efficacy and safety of APP remains controversial (Fleischhacker and Uchida, 2014; Lochmann van Bennekom et al., 2013; Galling et al., 2017; Taipale et al., 2023). Guidelines for the treatment of psychotic disorders therefore advocate antipsychotic monotherapy (APM) and advice to restrict APP to cross-titration during switching of antipsychotics, and as an option in patients with treatment-resistant schizophrenia (Moore et al., 2007; Kuipers et al., 2014; van Alphen et al., 2012; American Psychiatric Association, 2020).

Little is known about the relationship between clinician's initial reasons for initiating APP and the outcomes of APP over time. Most studies investigating the indications for APP are cross-sectional studies or retrospective chart reviews (Haw and Stubbs, 2003; Correll et al., 2011; Ajayi and Arora, 2023; James et al., 2017; Chang and Kim, 2014; Kishimoto et al., 2013). However, such studies are hampered by the fact that the indication for APP is assessed at only one point in time, by the risk of bias associated with retrospective information retrieval, and by the lack of accurate information from prescribers about the reasons for possible changes in indication or discontinuation of APP over time. More knowledge about the dynamic process of prescribing APP is important because it can contribute to a better understanding of

the development of persistent APP, including the extent to which this controversial treatment strategy is a deliberate choice or not.

The present cohort study was part of a larger prospective study aiming to reduce inappropriate APP in inpatients, which showed that the addition of an individualized intervention was effective in reducing episodes of persistent APP by almost 50% and reducing patient days on APP by 35% (Lochmann van Bennekom et al., 2021). In a consecutive cohort of patients with newly initiated APP, the present study aimed to examine the longitudinal course of indications for APP in relation to the initial indications, including the prevalence of ongoing APP due to unfinished cross-titration switching of antipsychotics.

Methods

Study design

The present prospective cohort study was part of a serial intervention study that we conducted in a 324-bed regional psychiatric hospital in the Netherlands, and that aimed to reduce inappropriate APP in inpatients (Lochmann van Bennekom et al., 2021). That study consisted of four stages lasting nine months each: 1) baseline, 2) application of a general intervention to reduce inappropriate APP, e.g., 3-monthly general e-mail with a guideline reference on APP, 3) application of a general + prescriber-focused intervention, e.g., addition of a personalized e-mail to each clinician who initiated a new prescription resulting in APP, and 4) follow-up. The present study was conducted in stage 3. At the beginning of this stage, all physicians in the institution were once more informed by e-mail about the ongoing study to reduce inappropriate APP, with the Dutch guidelines for the treatment of patients with schizophrenia attached. They were also informed about the additional personalized intervention, in which we asked the prescribing physician by e-mail for the indication for each new prescription that resulted in APP and repeated this after 30 and 60 days (for the content of these e-mails, see Supplemental Text 1, 2 and 3). If a patient had multiple episodes of APP, we included only the first episode in our analyses. We included prescriptions for a second antipsychotic to be used 'as needed' (PRN), assuming they were actually used, but excluded prescriptions for a second injectable antipsychotic to be given only in the event of refusal of the primary oral antipsychotic, because in such a case there is in fact no APP. All eleven psychiatrists and five residents associated with the hospital's adult inpatient units participated in the study. Three psychiatrists were assigned to the admission units, four to the rehabilitation units, and four to the elderly units for both admission and

rehabilitation. Overall, psychiatrists' clinical experience ranged from 2-20 years (mean 9.6). Early career psychiatrists were more likely to be assigned to adult admission wards (mean 5 years, range 2 – 11). Psychiatrists assigned to rehabilitation units had more clinical experience (mean 13.5 years, range 9 – 20), and psychiatrists assigned to elderly units had a mean of 9.3 years of clinical experience (range 2 – 20). As required in the Netherlands, all psychiatrists had board certification, which requires 20 hours of continuing medical education (CME) per year and must be renewed every 5 years to maintain registration as a medical specialist. There were no changes in psychiatrists during the study. Residents were supervised by the psychiatrists assigned to their ward and changed every 6 – 12 months according to their residency program.

Data collection

Immediately after each new antipsychotic prescription resulting in APP, regardless of diagnosis, the hospital pharmacy sent an e-mail to the prescribing physician on behalf of the first author with the patient's hospital identification number. In this e-mail we requested the reason for APP by asking the physician to select one of four options:

1. Switch of antipsychotics (cross-titration)
2. Sedation (because of agitation or sleep disorders)
3. Treatment refractory psychotic symptoms
4. Other reasons (with request to provide a specification).

If the prescribing physician did not respond within one week, we sent weekly reminder e-mails. After 30 and 60 days, we e-mailed the physician to ask if there was ongoing APP and, if so, for which of the abovementioned indications. If no ongoing APP was reported, we asked for the date the APP was discontinued. Again, if the prescriber did not respond within one week, we sent weekly reminder e-mails. Data on unfinished cross-titrations were extracted from cases of persistent APP at 60 days that were initially intended to switch antipsychotics. Because cross-titration switching of oral antipsychotics can usually be completed within 30 days, a 60-day period is more than sufficient to assess the completion of mutual switching of oral antipsychotics; however, switching from an oral antipsychotic to a long-acting injectable antipsychotic can take up to 12 weeks (Switching Antipsychotics, available at: http://wiki.psychiatrienet.nl/index.php/SwitchAntipsychotics, accessed March 13, 2024). Therefore, in the case of persistent APP at 60 days due to ongoing switching to long-acting injectable antipsychotics, we checked hospital pharmacy records for ongoing APP at 90 days before classifying such an episode as a case of unfinished cross-titration.

Outcome measures

Primary outcomes were indications for APP at initiation, 30 days, and 60 days. Secondary outcome was the proportion of unfinished cross-titration switches of antipsychotic at 60 days of all APP episodes initiated to switch antipsychotics.

Statistical analyses

Descriptive statistics were provided with the statistical package IBM SPSS, version 25.

Medical ethical issues

The study was conducted in accordance with the guidelines for Good Clinical Practice and was approved by the Institutional Review Board (IRB). The IRB considered the whole project, including the stage reported here, to be a quality improvement study aimed at improving adherence to guidelines in routine clinical practice by all physicians working at the hospital. Therefore, they did not consider informed consent from physicians involved necessary. Physicians remained free to choose which antipsychotic to prescribe, including APP, without any professional or personal consequences. The study was also reported to the institute's Patient Council. Because this observational study used only an anonymous patient identification number, informed consent from patients was not required.

Results

Study sample

During the nine-month study period, 484 patients were prescribed at least one antipsychotic, of whom 55 patients (11%), including 26 women and 29 men, were newly started on APP. The primary diagnosis among these patients was schizophrenia spectrum disorder (n=44; 80%), followed by borderline personality disorder (n=4; 7%), bipolar disorder (n=4; 7%), dementia (n=1; 2%), anxiety disorder (n=1; 2%), and adjustment disorder (n=1; 2%). These patients were prescribed 12 different primary antipsychotics, i.e., risperidone (16%), aripiprazole (13%), clozapine (13%), olanzapine (13%), quetiapine (13%), haloperidol (9%), penfluridol (7%), zuclopentixole (7%), pimozide (3%), fluphenazine (2%), flupentixol (2%) and levomepromazine (2%). These primary antipsychotics were combined with 15 additional antipsychotics, i.e., levomepromazine (18%), aripiprazole (16%), clozapine (16%), risperidone (9%), olanzapine (7%), quetiapine (7%), haloperidol (5%), pimozide (4%), pipamperone (4%), sulpiride (4%), flupentixole (2%), fluphenazine (2%), paliperidone (2%), penfluridol (2%), and zuclopentixole (2%). The clinical and educational backgrounds of the psychiatrists, the number of

patients they prescribed APP to, and the course of their prescribed APP are shown in Supplemental Table S1.

Course of APP

APP was initiated for switching of antipsychotics in 31 of 55 patients (56%), for sedation to reduce agitation or sleep problems in 12 patients (22%), and for treatment refractoriness in ten patients (18%).

Thirty days after initiation, APP was continued in 30/55 patients (55%) and discontinued in 25 patients (45%). Discontinuation of APP was mainly (20/25; 80%) because cross-titration switching of antipsychotics was completed. APP was discontinued in three patients (12%) because a sedating antipsychotic was discontinued, in one patient (4%) because an augmenting antipsychotic for treatment refractoriness was discontinued, and in one patient (4%) because APP for another reason (i.e., persistent mania) was discontinued.

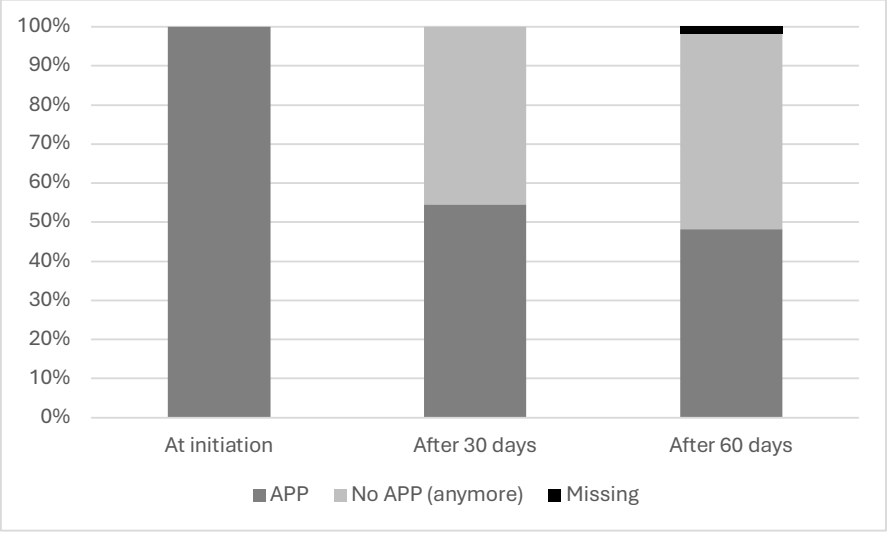

Figure 1 Course of newly initiated antipsychotic polypharmacy in 55 patients after 30 and 60 days.
APP = antipsychotic polypharmacy
Missing = no response from prescriber

Sixty days after initiation APP was continued in 27/55 patients (49%). Additional antipsychotics that were continued were levomepromazine (26%), aripiprazole (18%), clozapine (15%), quetiapine (11%), haloperidol (7%), pipamperone (7%), fluphenazine (4%), olanzapine (4%), risperidone (4%), and sulpiride (4%). Three additional episodes

of APP were discontinued, two because switching of antipsychotics was completed, and one because an additional sedating antipsychotic was no longer needed, resulting in 28 patients (51%) in whom APP was discontinued. For an overview see figure 1. Additional antipsychotics that were discontinued at 60 days were clozapine (17%), aripiprazole (14%), risperidone (14%), levomepromazine (10%), olanzapine (10%), pimozide (7%), flupentixol (4%), haloperidol (4%), paliperidone (4%), penfluridol (4%), quetiapine (4%), sulpiride (4%), and zuclopentixol (4%). Persistent APP tended to be more common in more experienced physicians working in adult rehabilitation units (see Supplemental Table S1).

Indications for APP over time

As noted, primary indication to initiate APP was switching antipsychotics in 31/55 patients, followed by sedation to reduce agitation or sleep problems in12/55 patients, and treatment refractoriness in 10/55 patients. In two patients another reason was reported, i.e., persistent mania.

After 30 days there were 30 patients with persistent APP. Switching of antipsychotics was still the most common reason for continuing APP in 11/30 patients, followed by sedation and treatment refractoriness both in 9/30 patients. In one patient APP was continued because of persistent mania. After 60 days, there were 27 patients with persistent APP. The distribution of indications was very similar to that at 30 days, with ongoing switching of antipsychotics in nine patients, treatment refractoriness in eight patients, and sedation in seven patients. In two patients, APP was continued for other reasons, one because of persistent mania and one because the patient refused to discontinue the second antipsychotic that was initiated because of refractory psychotic symptoms. In one patient the indication for APP after 60 days was not reported. At 60 days, APP initiated for switching antipsychotics was ongoing in 9/31 patients (29%), APP initiated for sedation was ongoing in 8/12 patients (66%), and APP initiated for refractoriness was ongoing in 9/10 patients (90%).

An overview of the indications for APP at initiation, 30 days, and 60 days is provided in Figure 2.

Consistency in initial indication for APP

Consistency after 30 days

Thirty days after initiation, in 30 episodes of persistent APP, the initial indication of switching of antipsychotics was maintained in 10/11 patients, and the indication

changed to treatment refractoriness in one patient. In all nine patients with APP initiated because of sedation the indication was maintained. In 9/10 patients with APP initiated for treatment refractoriness the indication was maintained, in one patient the indication was changed to switching of antipsychotics.

Consistency after 60 days

After 60 days, in the remaining 27 episodes of persistent APP, the initial indication of switching of antipsychotics was maintained in 8/9 patients, in one patient the indication changed to treatment refractoriness because the patient was doing better on the combination. In 7/8 patients with APP initiated because of sedation the indication was maintained, in one patient the indication was changed to refractoriness. In 6/9 patients with APP initiated because of treatment refractoriness the indication was maintained, in one patient the indication was, remarkably, changed from refractoriness back to the original indication of switching of antipsychotics, in one patient the indication was changed to "other reason" (i.e., the patient refused to discontinue an antipsychotic), and in one patient the indication was not reported.

After 60 days, APP initiated for cross-titration switching of antipsychotics was continued in 8/31 patients (26%), APP initiated for sedation was continued in 7/12 patients (58%), and APP initiated for refractoriness was continued in 6/10 patients (60%).

An overview of the changes in indications over time is provided in Figure 2.

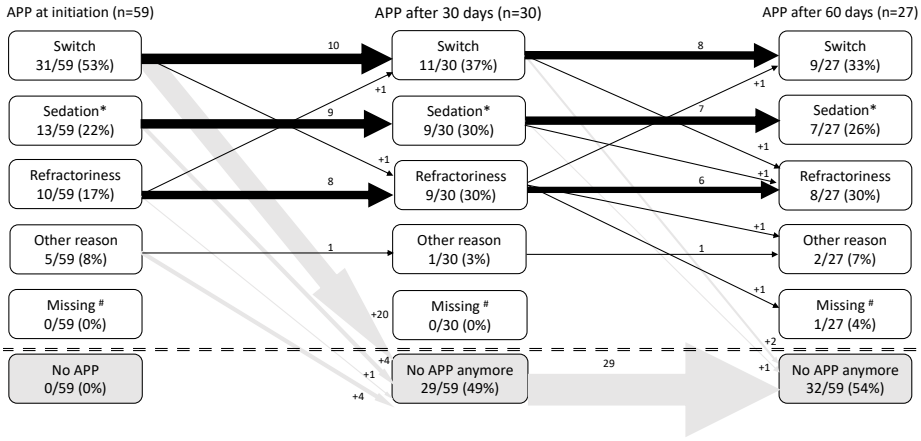

Figure 2 Course of indications over time in 55 patients with newly initiated antipsychotic polypharmacy.
**APP=antipsychotic polypharmacy. *Sedation = agitation /sleep disorders. #Missing = not reported by prescriber.
**The width of the arrows represents the number of patients transitioning from the initial indication to the indication at follow-up.

Unfinished cross titrations

Of the 31 patients with APP initiated to switch antipsychotics, eight patients were still on APP for this indication at 60 days, including one patient with an intermediate change of indication to refractory at 30 days. In one patient the initial indication switching of antipsychotics eventually changed to treatment refractoriness, which is also a case of unfinished cross-titration. There were no patients switching from an oral to a long-acting antipsychotic, so there was no need to check for ongoing APP at 90 days. As a result, 9/31 patients (29%) met the criterion for unfinished cross-titration.

Discussion

To our knowledge, this is the first prospective study to examine clinicians' indications for initiating APP and how these indications change over time. In a consecutive cohort of 55 inpatients primarily diagnosed with schizophrenia spectrum disorders who were newly initiated on APP, we assessed clinicians' initial indications for this treatment strategy, adherence to this indication at 30 and 60 days, and the prevalence of unintended APP due to unfinished cross-titrations. We found that switching of antipsychotics was the dominant indication for starting APP, occurring in more than half of the cases, followed by sedation to reduce agitation or sleep problems, and the treatment of refractory symptoms. APP was continued in 55% of patients at 30 days and in 49% at 60 days. Continuation at 60 days occurred in 29% of the patients in whom it was initiated for switching. If APP was continued, it was mostly because of the same reason as the reason for indication.

Our results show that in most patients with newly initiated APP, this was due to antipsychotic switching. As part of an intervention to reduce inappropriate APP, this switching process was completed within 30 days in the majority of these patients, consistent with recommendations for switching to another oral antipsychotic (see: http://wiki.psychiatrienet.nl/index.php/SwitchAntipsychotics). Interestingly, APP for antipsychotic switching as a primary indication at initiation but also at follow-up has not been previously reported in the literature, where persistent APP is typically associated with refractory symptoms (Sernyak and Rosenheck, 2004; Gallego et al., 2012). This may be explained by our prospective design, which includes only newly initiated APP, in contrast to previous cross-sectional studies in which persistent and sometimes 'inherited' APP is much more common. In addition, if a patient improves during the switching process and continues to have persistent APP, a prescriber

may be more likely to report in retrospect that this was due to refractory symptoms rather than the originally intended antipsychotic switch.

APP appeared to be a predominantly intentional and consistent treatment strategy in this cohort. Prescribers maintained their initial indication for APP in 78% of patients with persistent APP at 60 days. In particular, APP initiated for refractoriness was rarely discontinued and remained consistently prescribed over time, contrary to the advice in current guidelines. Previous research has shown that routine clinical practice often deviates from these guidelines, switching to a new antipsychotic too early without exploring the full dose range, and opting for antipsychotic polypharmacy without trying an adequate number of antipsychotics, which is often continued once started (Tsutsumi et al., 2011; Shinfuku et al., 2012). However, it should also be noted that there is emerging evidence that APP may be effective in some difficult-to-treat patients with psychotic disorders (Bighelli et al., 2022), but the lack of data on the clinical condition and treatment history of the patients in our sample does not allow us to conclude whether non-adherence to these guidelines was justified or not. Although the majority of patients that were prescribed APP due to antipsychotic switching completed this switch and discontinued APP, in 29% of these patients APP was continued, and the treatment was "trapped" in cross-titration. This was often because the prescriber noted that the patient was doing better on the combination, sometimes because the patient refused to discontinue the primary antipsychotic. The percentage of unfinished cross-titrations that we found is lower than that reported in two previous retrospective chart reviews from hospitals in the United States (Sernyak and Rosenheck, 2004; Tapp et al., 2003). The first 12-month study investigated APP with at least one “atypical” antipsychotic, excluding clozapine combinations, in 66 outpatients diagnosed with schizophrenia and found unfinished cross-titration in 14/26 patients (54%) at 6 to 12 months follow-up (Sernyak and Rosenheck, 2004). The second 6-month study evaluated 39 outpatients, predominantly diagnosed with schizophrenia, who had been on APP for more than 30 days and found unfinished cross-titration in 12/15 patients (80%) who switched from a “conventional” antipsychotic to an “atypical” antipsychotic (Tapp et al., 2003). The lower rate we found may be best explained by the ongoing intervention to reduce inappropriate APP in which this study was embedded, and thus may be an underestimate of the number of uncompleted cross-titrations in routine clinical practice. Another explanation may be the prospective design of our study, which allowed for more accurate registration of indications over time compared to a retrospective design.

Strengths of our study are the prospective design with inclusion of all newly initiated episodes of APP, the comprehensive data collection, and the very low number of missing data. There are also some limitations to consider. First, the generalizability of our findings is limited because the study was conducted in the context of an assertive intervention aimed at reducing inappropriate APP. Assertive interventions have shown to be effective in reducing APP (Tani et al., 2013), and this may have caused clinicians to be more critical in indicating and continuing APP compared to routine clinical practice. However, even within this context, APP due to treatment refractoriness and uncompleted cross-titrations remained high. Gradual cross-titration switching of antipsychotics is often recommended to avoid rebound and/or withdrawal syndromes, but a systematic review and meta-analysis found no significant differences in clinical outcomes between immediate discontinuation and a gradual tapering approach (Takeuchi et al., 2017). Although switching of antipsychotics always needs to be individualized for each patient, this brings up the opportunity to switch antipsychotics more abruptly in order to avoid a cross-titration process that may result in unnecessary APP. Another limitation is the lack of information on previous medications and the clinical status of the patients involved, which hinders a better weighting of the appropriateness of clinicians' indications for persistent APP. This clinical information is important for future research, especially in difficult-to-treat psychotic patients, given recent studies that provide some evidence for the efficacy of APP in this population (Tiihonen et al., 2019; Lahteenvuo and Tiihonen, 2021; Bighelli et al., 2022).

Conclusion

In this prospective study of a consecutive cohort, APP was initiated primarily for cross-titration switching of antipsychotics and, to a lesser extent, to reduce agitation and/or sleep problems or to treat refractory psychotic symptoms. This study was conducted as part of a prospective intervention trial to reduce inappropriate combined antipsychotic prescribing. APP appeared to be a deliberate and consistent treatment strategy over time, especially when initiated for treatment refractoriness, albeit beyond guideline recommendations. Although most patients with APP that was initiated for cross-titration switching of antipsychotics completed the switch within 30 to 60 days, in 29% of patients switching was not completed and patient and prescriber were "trapped" in cross-titration, resulting in unintended and potentially unnecessary persistent APP. This may still be an underestimate of the numbers in routine daily clinical practice, and points to a qualitative problem in the prescribing of antipsychotics in difficult-to-treat patients with psychotic disorders.

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Supplemental Material

Antipsychotic polypharmacy in time course: evidence for a cross-titration trap

Marc W.H. Lochmann van Bennekom, Harm J. Gijsman, Joanna IntHout, and Robbert Jan Verkes

J Clin Psychopharmacol. 2024 Nov-Dec; 44(6)545-550

List of Supplemental Material

1. Supplemental Text mail 1: Initial mail APP to prescriber
2. Supplemental Text mail 2: Follow-up mail at 30 days
3. Supplemental Text mail 3: Follow-up mail at 60 days
4. Supplemental Table S1: Demographics of 11 psychiatrists

Supplemental Text 1: Initial mail APP to prescriber (translated)

Dear colleague,

Daily medication monitoring by the supervising pharmacy ZALV shows that you have started to prescribe 2 antipsychotics at the same time. You are receiving this alert email from ZALV as part of my study to reduce unnecessary antipsychotic polypharmacy (APP), about which I informed all physicians of the GGz Nijmegen on July 1, 2009. In this context, I offer the following advice for your consideration:

1. *APP may be necessary for a short period of time (usually < 30 days) when changing antipsychotics.*
2. *The addition of a second, often low-dose, sedating antipsychotic (including levomepromazine) is sometimes used temporarily for agitation or sleep disturbances. This policy is under discussion and is not according to current guidelines.*
3. *It is recommended that long-term APP (> 30 days) be used at most in patients who do not or respond inadequately to adequate treatment trials with two different antipsychotics followed clozapine, and that the combination be continued only if there is clear improvement.*

REQUEST

As part of the study, I would also like to know from you via the following e-mail address mlochmannvanbennekom@ggznijmegen.nl with what indication you prescribe two antipsychotics:

1. *Switching antipsychotics*
2. *Agitation/sleep disturbance*
3. *Treatment-resistant symptoms*
4. *Other reason, i.e.:*

I hope this information has been helpful and look forward to hearing from you. Please do not hesitate to contact me.

Marc Lochmann van Bennekom, psychiatrist
mlochmannvanbennekom@ggznijmegen.nl

Supplemental Text 2: Follow-up mail at 30 days (translated)

Patient ID: …….

Dear Colleague,

The above patient was started 30 days ago with simultaneous prescription of 2 antipsychotics, initiated because of …….

As part of my research, I have 3 questions:

1. *Is he/she still using the combination? If not, when was what stopped?*

2. *Is the indication still ……., or does one of the other 3 indications now apply?*
    1. *Switch*
    2. *Agitation/sleep disorder*
    3. *Therapy-resistant symptoms*
    4. *Other reason, i.e: …….*

3. *Does the result make it desirable to continue the combination?If the combination is still ongoing, I would be happy to make an appointment for consultation, if you wish.*

Thank you in advance for your response.

Yours sincerely,
Marc Lochmann van Bennekom

Supplemental Text 3: Follow-up mail at 60 days (translated)

Patient ID: …….

Dear Colleague,

The above patient was started 60 days ago with simultaneous prescription of 2 antipsychotics, initiated because of …….
As part of my research, I have 3 questions:

1. Is he/she still using the combination? If not, when was what stopped?

2. Is the indication still ……, or does one of the other

3 indications now apply?

1. *Switch*
2. *Agitation/sleep disorder*
3. *Therapy-resistant symptoms*
4. *Other reason, i.e: …….*

3. Does the result make it desirable to continue the combination?

If the combination is still ongoing, I would be happy to make an appointment for consultation, if you wish.

Thank you in advance for your response.
Yours sincerely,

Marc Lochmann van Bennekom

Supplemental Table S1: Demographics of 11 psychiatrists

Table S1 Demographics of 11 psychiatrists involved and the course of the APP the prescribed.

Psychiatrist	Sex	Years of registration per 01-01-2011	Unit	Resident at the unit?	Patients initiated on APP	Patients with persistent APP at 60 days	Patients with unfinished cross-titration
1	F	2	Admission adults	Yes	8	1 (13%)	0
2	F	5	Elderly	Yes	2	1 (50%)	0
3	F	10	Elderly	No	2	0 (0%)	0
4	M	2	Admission adults	Yes	3	0 (0%)	0
5	M	20	Rehabilitation adults	No	11	10 (91%)	4
6	M	11	Admission adults	Yes	10	3 (30%)	0
7	F	15	Rehabilitation adults	Yes	9	6 (67%)	0
8	M	20	Elderly	No	2	1 (50%)	1
9	F	9	Rehabilitation adults	Yes	5	2 (40%)	0
10	F	2	Elderly	Yes	1	0 (0%)	0
11	F	10	Rehabilitation adults	Yes	2	2 (100%)	0
	F=64% M=36%	Mean: 9.6, range 2 – 20			55	26 (missing: 1)	5 (missing: 1)

Chapter 6

Efficacy and Tolerability of Antipsychotic Polypharmacy for Schizophrenia-Spectrum Disorders.

A Systematic Review and Meta-Analysis of Individual Patient Data

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Schizophr Res. 2024 Oct;272:1-11.

Abstract

Background: Antipsychotic polypharmacy (APP) is frequently prescribed for schizophrenia-spectrum disorders. Despite the inconsistent findings on efficacy, APP may be beneficial for subgroups of psychotic patients. This meta-analysis of individual patient data investigated moderators of efficacy and tolerability of APP in adult patients with schizophrenia-spectrum disorders.

Design: We searched PubMed, EMBASE, and the Cochrane Central Register of Randomized Trials until September 1, 2022, for randomized controlled trials comparing APP with antipsychotic monotherapy. We estimated the effects with a one-stage approach for patient-level moderators and a two-stage approach for study-level moderators, using (generalized) linear mixed-effects models. Primary outcome was treatment response, defined as a reduction of 25% or more in the Positive and Negative Syndrome Scale (PANSS) score. Secondary outcomes were study discontinuation, and changes from baseline on the PANSS total score, its positive and negative symptom subscale scores, the Clinical Global Impressions Scale (CGI), and adverse effects.

Results: We obtained individual patient data from 10 studies (602 patients; 31% of all possible patients) and included 599 patients in our analysis. A higher baseline PANSS total score increased the chance of a response to APP (OR=1.41, 95% CI 1.02; 1.94, p=0.037 per 10-point increase in baseline PANSS total), mainly driven by baseline positive symptoms. The same applied to changes on the PANSS positive symptom subscale and the CGI severity scale. Extrapyramidal side effects increased significantly where first and second-generation antipsychotics were co-prescribed. Study discontinuation was comparable between both treatment arms.

Conclusions: APP was effective in severely psychotic patients with high baseline PANSS total scores and predominantly positive symptoms. This effect must be weighed against potential adverse effects.

Introduction

Schizophrenia and other psychotic disorders are severe, disruptive psychiatric disorders. Since decades, dysregulation of dopaminergic functioning has been postulated as a central explanatory model, assuming that striatal presynaptic hyperdopaminergia involving D_2 receptors underlies psychotic symptoms and cortical hypodopaminergia involving D_1 receptors underlies cognitive symptoms in schizophrenia, and reducing striatal hyperdopaminergia is a considered to be a key mechanism of action in treating positive symptoms of schizophrenia (McCutcheon et al., 2020; Kaar et al., 2020). All approved antipsychotic medications reduce dopaminergic transmission, generally by blocking 60-80% of postsynaptic dopamine D_2 receptors in the striatal region of the brain (Kaar et al., 2020), although clozapine, with its evidence-based superior efficacy in treatment-resistant psychosis, has only modest affinity for the D_2 receptor. However, treatment-resistant symptoms persist in approximately 40% of patients, despite multiple antipsychotic monotherapies, including clozapine (Diniz et al., 2023), prompting clinicians to consider alternative treatments, including antipsychotic polypharmacy (APP). APP is the concurrent use of at least two different antipsychotic medications for a patient and is frequently prescribed in approximately 20% of patients with a psychotic disorder (Gallego et al., 2012). Clinicians' attitudes towards APP are heterogenous (Correll et al., 2011; Ajayi and Arora, 2023; James et al., 2017; Chang and Kim, 2014; Kishimoto et al., 2013), but the main reason for prescribing APP is to treat refractory psychotic symptoms (Sernyak and Rosenheck, 2004; Correll and Gallego, 2012). This strategy has been based on various hypotheses: a pharmacodynamic hypothesis (combining antipsychotics with different receptor profiles, e.g., clozapine with an antipsychotic with high D_2 receptor affinity like sulpiride); a pharmacokinetic hypothesis (drug-drug interactions resulting in higher antipsychotic plasma levels); an acute-phase hypothesis (temporarily combining a sedating antipsychotic with a non-sedating antipsychotic in acutely exacerbated psychotic patients); and/or an adherence hypothesis (adding a second antipsychotic may mitigate the adverse effects of the primary medication) (Guinart and Correll, 2020; Azorin and Simon, 2020). However, the scientific evidence supporting these hypotheses is limited and the clinical evidence for the efficacy and safety of APP is controversial (Fleischhacker and Uchida, 2014; Lochmann van Bennekom et al., 2013; Galling et al., 2017). The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia and all international guidelines therefore advocate antipsychotic monotherapy (APM), including an adequate treatment trial of clozapine for treatment-resistant psychotic disorder, and state that there is only weak and inconsistent evidence for benefit with APP in treating patients with

treatment-resistant schizophrenia (American Psychiatric Association, 2020; Correll et al., 2022). Nevertheless, there is some evidence from systematic reviews and meta-analyses that APP may be superior to APM in subgroups of patients, e.g., inpatients, patients with more hospitalizations, higher illness severity, and a low initial Global Assessment of Functioning (GAF) score, or in acutely exacerbated patients (Correll et al., 2009; Galling et al., 2017; Paton et al., 2007; Taylor and Smith, 2009; Taylor et al., 2012; Wang et al., 2010; Ortiz-Orendain et al., 2017; Bighelli et al., 2022). These subgroups may reflect the selection of patients with a more severe psychotic illness.

Compared with a traditional study-level meta-analysis, an individual patient data meta-analysis (IPDMA) offers important advantages, including granularity and statistical power, for the investigation of the impact of these potential effect moderators (Hannink et al., 2013). Here, we describe the results of the first IPDMA, to our knowledge, investigating the efficacy and safety of APP versus APM in adult patients with schizophrenia-spectrum disorders. Our aim was to determine whether there were patient and study characteristics that were associated with a better outcome with APP.

Materials and methods

Registration

The study was preregistered at PROSPERO (CRD42015009464).

Eligibility criteria

Eligible were individual patient data (IPD) from all double-blind randomized placebo-controlled trials (RCTs) comparing any combination of registered antipsychotic medications with APM in patients aged 18 years or older, at least 80% of whom had a schizophrenia-spectrum diagnosis (i.e., schizophrenia, schizoaffective disorder, schizophreniform disorder, acute psychotic disorder, and psychotic disorder not otherwise specified). To quantify the outcome, studies had to assess the severity of positive and/or negative symptoms using a recognised rating scale. We also included studies combining antipsychotic medications to reduce side effects and studies converting APP to monotherapy. We set no language restrictions.

Identification and selection of studies

We performed a comprehensive computerized systematic literature search in PubMed, EMBASE, and the Cochrane Central Register of Randomized trials from their inception until September 1, 2022. In addition, we searched for eligible

studies in reference lists, meeting abstracts, trial registers, and by word of mouth. For the search strategy see supplementary Table S1. Two researchers (MLvB, HG) independently reviewed title and abstract of the identified studies. Studies in Chinese were reviewed with the assistance of a Chinese translator (LX). Unless the study unanimously was excluded by title and abstract, the full text was reviewed and discussed for eligibility until consensus was reached.

Data collection, extraction, and standardization

We asked the first authors or other authors of the eligible studies to share with us their anonymized primary data. We sent monthly reminders, if there was no response after 12 weeks the trial was considered as unavailable. We extracted relevant data from the acquired datasets (supplementary Methods S1) and merged these in a new data set, that we analyzed. To make different psychopathology outcome scales mutually comparable, we applied established formulas to convert scores into total Positive and Negative Syndrome Scale (PANSS) scores, and PANSS positive symptom subscale and/or negative symptom subscale scores. We recalculated total antipsychotic end dose in olanzapine dose equivalents. For the formulas, see supplementary Table S2. Patients were considered dropout if this was registered as such in the IPD or (if such record was not available) no measurement had been recorded at the last visit.

Quality assessment

We checked the integrity of IPD by visual and digital inspection on completeness and consistency. Discrepancies were resolved with the original study authors. We used the Cochrane Risk of Bias 2 tool (RoB 2) to assess the risk of bias in individual studies (Higgins, 2021). We assessed potential selection bias by comparing key baseline characteristics of eligible studies from which we could and could not include IPD and attempted to assess the risk of publication bias.

Statistical analyses

The primary outcome was clinically relevant response, defined as a reduction of at least 25% in total PANSS score, at primary study endpoint (see also supplementary Methods S2). This is an accepted, clinically meaningful, effect in patients with refractory psychotic disorder (Leucht et al., 2009; Leucht et al., 2006). Analyses of response were performed without discontinuation studies, because in these studies a difference in response does not adequately reflect the efficacy of APP versus APM. Secondary outcomes were the mean change from baseline on the PANSS total and the PANSS positive and negative symptom subscales, and changes on the Clinical Global Impressions scales for severity (CGI-S) and improvement (CGI-I). For the CGI-I

subscale, we considered a rating of at least 'minimally improved' (ratings 1-3) as a clinically meaningful effect (Leucht et al., 2009; Leucht et al., 2006). When analyzing the CGI-I data, we also excluded discontinuation studies, for the aforementioned reason. Further outcomes were the frequency and severity of adverse effects and all-cause discontinuation. Potential moderators of effect that we investigated were:

1) Study aim (refractory psychotic symptoms, treating adverse effects, discontinuation of APP)
2) Study region (Europe, North America, Asia)
3) Illness stage (first episode, recurrent with acute exacerbation, chronic, refractory)
4) Illness duration
5) Illness severity at baseline
6) Setting (inpatient/outpatient)
7) Combinations of antipsychotic medications
8) Sex
9) Age

Analyses were performed on an intention-to-treat basis, as close as possible to 12 weeks after randomization, and with the last observation carried forward if needed. Effects of patient-level characteristics were analyzed with a centered one-stage approach to prevent ecological bias (Belias et al., 2019), with (generalized) linear mixed-effects models, after evaluation of possible nonlinear effects (supplementary Methods S3). Interaction coefficients of the potential moderators and subgroup results were summarized in forest plots, based on original units, and for the change in PANSS scores, also based on standardized mean differences (SMDs). Sensitivity analyses were performed to evaluate the robustness of the findings; 1) selecting the 1–99% quantile of the continuous modifier values to exclude outliers and 2) for secondary (continuous) outcomes excluding discontinuation studies (that may include an enriched population of patients that responded to and tolerated APP). Secondary outcomes, except those on psychopathology and extrapyramidal side effects (EPS), were reported using descriptive statistics. We applied the PRISMA-IPD checklist (Stewart et al., 2015) to report the study (supplementary Table S3) and the GRADE methodology (Atkins et al., 2004) to rate the evidence (supplementary Table S4). Analyses were performed with the statistical packages SPSS (version 25), and R version 4.2.2. (R Core Team, 2022).

Medical ethical issues

Since this IPDMA study uses anonymous data from approved studies, no new institutional review board approval was required.

Results

Study selection

Our search yielded 2075 papers, from which we identified 31 non-overlapping eligible studies with 1957 patients. We obtained IPD from 10 studies (32%), comprising 602 patients (31%). IPD from 21 studies were not obtained: from four studies, authors were interested to participate but no data were received; from another four studies IPD were not available for various reasons; from two studies, authors refused cooperation; and from 11 studies we received no response at all (Supplementary Table S6). We excluded IPD from three patients (one from the study by Mossaheb and colleagues (Mossaheb et al., 2006) and two from the study by Kreinin and colleagues (Kreinin et al., 2006)) because of dropout before randomization, finally resulting in 599 patients. For the study flow diagram, see Figure 1.

Study and patient characteristics

The included 10 IPD were related to nine 2-arm RCTs (Anil Yagcioglu et al., 2005; Barnes et al., 2018; Borlido et al., 2016; Gunduz-Bruce et al., 2013; Kreinin et al., 2006; Mossaheb et al., 2006; Nielsen et al., 2012a; Repo-Tiihonen et al., 2012; Shafti, 2009), and one 3-arm RCT (Schmidt-Kraepelin et al., 2022) published from 2005–2022. Seven studies investigated the effects of APP on refractory psychotic symptoms (one in acutely exacerbated, not clozapine-resistant patients (Schmidt-Kraepelin et al., 2022), six were in patients with treatment-resistant illness (Anil Yagcioglu et al., 2005; Barnes et al., 2018; Gunduz-Bruce et al., 2013; Mossaheb et al., 2006; Nielsen et al., 2012a; Shafti, 2009), two were 'discontinuation' studies, converting APP to APM (Borlido et al., 2016; Repo-Tiihonen et al., 2012), and one study aimed to reduce the side effects (hypersalivation) of the primary antipsychotic medication (Kreinin et al., 2006). Study endpoints ranged from 3–12 weeks. Two studies (Repo-Tiihonen et al., 2012; Kreinin et al., 2006) applied a cross-over design; we included only the first phase to avoid possible carry-over effects (Elbourne et al., 2002). All patients were diagnosed with schizophrenia or schizoaffective disorder. Seven studies (including one discontinuation study) investigated combinations of clozapine with a second antipsychotic (Anil Yagcioglu et al., 2005; Barnes et al., 2018; Gunduz-Bruce et al., 2013; Kreinin et al., 2006; Mossaheb et al., 2006; Nielsen et al., 2012a; Repo-Tiihonen et al., 2012), two studies investigated non-clozapine combinations (Schmidt-Kraepelin et al., 2022; Shafti, 2009), and one study investigated discontinuation of miscellaneous APP combinations (Borlido et al., 2016). To measure psychopathology, studies used the PANSS (Kay et al., 1987), the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1990), the Scale for the Assessment of Negative Symptoms

(SANS) (Andreasen, 1990), and the Clinical Global Impressions scale (CGI) (Guy, 1976). Side effects were measured mainly with the Simpson-Angus extrapyramidal side effects Scale (SAS) (Simpson and Angus, 1970), the Barnes Akathisia Rating Scale (BARS) (Barnes, 1989), and the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976). Inspection of the IPD revealed one unlikely PANSS total score that was corrected after consensus with the original researchers. The characteristics of the studies that provided the IPD are reported in Table 1. The baseline characteristics of the included patients are reported in supplementary Table S5. The characteristics of the 21 studies for which we could not obtain IPD are reported in supplementary Table S6. To assess the risk of selection bias we compared the characteristics of studies from which we could and could not obtain IPD. This showed that studies investigating the efficacy of APP were equally represented in approximately 30% of studies, European studies were over-represented and North American studies were under-represented in our sample. Mainly, eligible studies investigated clozapine combinations for treatment refractory illness, that were equally represented (supplementary Table S7).

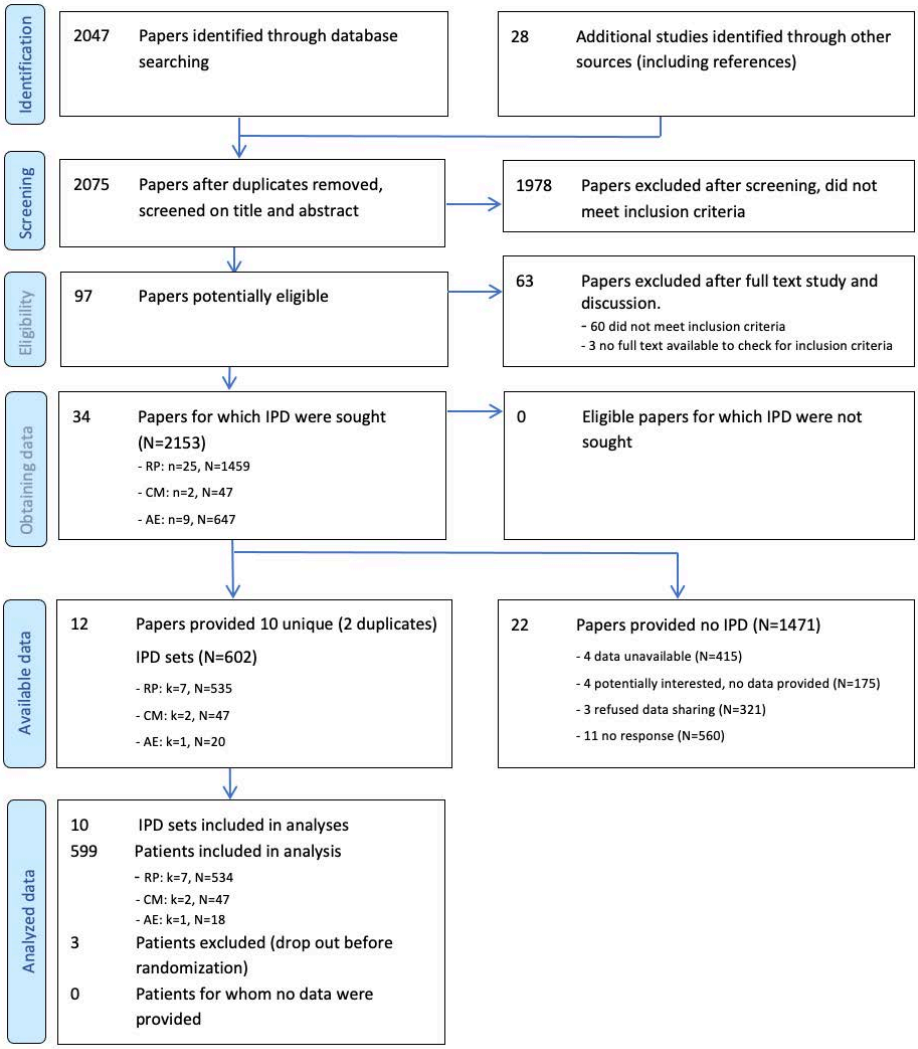


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Patient Data (PRISMA-IPD) Flow Diagram (final search: September 1, 2022) Legend: AE= studies in patients with adverse effects, CM= studies converting antipsychotic polypharmacy to monotherapy, IPD=individual patient data, k=number of patient data sets, n=number of papers, N=number of participants, RP= studies in patients with refractory psychosis.

The PRISMA IPD flow diagram © Reproduced with permission of the PRISMA IPD Group, which encourages sharing and reuse for non-commercial purposes. (Source: http://www.prisma-statement.org/Extensions/IndividualPatientData)

Table 1 Characteristics of the included studies

	Study	Study region (country)	n (I/C)	Intervention vs comparison	Mean (SD) antipsychotic dose in milligram OLA-eq (APP; APM)	Primary endpoint
Clozapine combinations						
1	(Anil Yagcioglu et al., 2005) / (Akdede et al., 2006)	West Asia (Turkey)	30 (16/14)	CLOZ + RIS vs. CLOZ	27.80 (5.77); 13.81 (3.23)	6w
2	(Barnes et al., 2018)	Europe (UK)	68 (35/33)	CLOZ + AMI vs. CLOZ	26.61 (6.46); 12.46 (4.83)	12w
3	(Gunduz-Bruce et al., 2013)	North America (US)	28 (14/14)	CLOZ + PIM vs CLOZ	Unknown	12w
4	(Kreinin et al., 2006)	West Asia (Israel)	20 (9/11)	CLOZ + AMI vs. CLOZ	Unknown	3w
5	(Mossaheb et al., 2006)	Europe (Austria)	10 (3/7)	CLOZ + HAL vs. CLOZ	19.75 (2.12); 15.00 (2.12)	10w
6	(Nielsen et al., 2012a) / (Nielsen et al., 2012b)	Europe (Denmark)	50 (25/25)	CLOZ + SER vs. CLOZ	21.90 (4.44); 13.05 (5.93)	12w
non-clozapine combinations						
7	(Schmidt-Kraepelin et al., 2022)	Europe (Germany)	321 (110/102 /109)	OLA + AMI vs. OLA vs. AMI	28.28 (11.80); 14.13 (5.56); 16.99 (6.86)	8w
8	(Shafti, 2009)	West Asia (Iran)	28 (14/14)	OLA + FLU-DEC vs. OLA	Unknown	12w
Discontinuation studies						
9	(Borlido et al., 2016)	North America (Canada)	35 (17/18)	APP vs. APM	19.92 (9.88) median 18.34; 20.72 (16.62) median 14.71)	12w

	Aim and study population	Psycho-pathology outcome scales	Other scales	Conclusion
	Reducing refractory psychotic symptoms in in- and outpatients with schizophrenia, insufficiently responding to clozapine.	PANSS, CGI-S, CDS	SAS, AIMS, BAS, UKU, RAVLT, COWAT, DST, GAF, QoL-21	No significant benefit for APP with respect to psychopathology and cognitive functioning.
	Reducing refractory psychotic symptoms in in- and outpatients with schizophrenia, insufficiently responding to clozapine (PANSS ≥ 80).	PANSS, CDS	SAS, AIMS, BARS,	No significant differences in therapeutic efficacy between both groups.
	Reducing refractory psychotic symptoms in outpatients with schizophrenia or schizoaffective disorder, insufficiently responding to clozapine (BPRS ≥ 35).	SANS, BPRS, CGI-S, CGI-I	SAS, AIMS, RAVLT, COWAT, DST	No beneficial effect of APP.
	Reducing hypersalivation in clozapine treated inpatients with schizophrenia.	PANSS, CGI-S, CGI-I	SAS, NHRS,	Significant improvement for APP group on the PANSS negative symptoms subscale, not on other subscales of the PANSS
	Reducing refractory psychotic symptoms in patients with schizophrenia, insufficiently responding to clozapine.	PANSS, CGI-S, CGI-I	SAS, AIMS, BARS	No significant difference in PANSS total scores between both groups.
	Reducing refractory psychotic symptoms in patients with schizophrenia, insufficiently responding to clozapine.	PANSS, CGI-S, CGI-I	UKU, QoL-26, GAF	APP was not superior to monotherapy.
	Reducing psychotic symptoms in inpatients with non-first episode schizophrenia or schizoaffective disorder (PANSS ≥ 70, at least two positive subscale items rated ≥ 4), excluding patients with a history of clozapine failure.	PANSS, CGI-S, CGI-I	SAS, DOTES, DISF-SR, SWN-S	AMI +OLA was significantly more effective than OLA monotherapy. No significant difference was observed between AMI + OLA and AMI monotherapy.
	Reducing psychotic symptoms in female inpatients with schizophrenia insufficiently responsive to olanzapine.	SANS, SAPS, CGI-S	SAS	APP was significantly more effective than monotherapy on SAPS and CGI-S outcomes.
	Conversion to monotherapy in in- and outpatients with schizophrenia or schizoaffective disorder ≥ 30 days on APP	BPRS, CGI-S, CGI-I	SAS, AIMS, BARS	Almost 80% could be safely transitioned from APP to APM with no clinical deterioration.

Table 1 Continued

	Study	Study region (country)	n (I/C)	Intervention vs comparison	Mean (SD) antipsychotic dose in milligram OLA-eq (APP; APM)	Primary endpoint
10	(Repo-Tiihonen et al., 2012)	Europe (Finland)	12 (5/7)	CLOZ + OLA vs. CLOZ	42.85 (8.28); 17,14 (6,52)	12w

Legend: AIMS=Abnormal Involuntary Movement Scale, AMI=amisulpride, APP=antipsychotic polypharmacy, ARI=aripiprazole, BARS=Barnes Akathisia Rating Scale, BPRS=Brief Psychiatric Rating Scale, CDS=Calgary Depression Scale, CGI-I=Clinical Global Impressions Improvement scale, CGI-S=Clinical Global Impressions Severity scale, CLOZ=clozapine, COWAT=Controlled Word Association Test, DISF-SR=Derogatis Interview for Sexual Functioning–Self Reporting, DOTES=Dosage Record and Treatment Emergent Symptom Scale, DST=Digit Span Test, FLU-DEC=fluphenazine decanoate, GAF=Global Assessment of Functioning, HAL=haloperidol, n(I/C)=total number of patients (number allocated to intervention arm/number allocated to control arm), NHRS=Nocturnal Hypersalivation Rating Scale, OLA=olanzapine, OLA-eq=olanzapine equivalent, PANSS=Positive and Negative Syndrome Scale, p.e.=primary endpoint, PIM=pimozide, QoL-21=Quality of Life scale 21 items, QoL-26=Quality of Life scale 26 items, RAVLT=Rey Auditory Verbal Learning Test, RIS=risperidone, SANS=Scale for the Assessment of Negative Symptoms, SAPS=Scale for the Assessment of Positive Symptoms, SAS=Simpson-Angus extrapyramidal side effects Scale, SER=sertindole, SWN-S=Subjective Wellbeing under Neuroleptics Scale–Short form, UKU=Udvalg for Kliniske Undersøgelser side effect rating scale.

Risk of bias

The overall risk of bias of included studies according the RoB 2 tool was assessed as low in four studies (Anil Yagcioglu et al., 2005; Barnes et al., 2018; Borlido et al., 2016; Schmidt-Kraepelin et al., 2022), with some concerns in two studies (Nielsen et al., 2012a; Shafti, 2009), and a high risk in four studies (Gunduz-Bruce et al., 2013; Kreinin et al., 2006; Mossaheb et al., 2006; Repo-Tiihonen et al., 2012) (supplementary Table S8). The number of studies was too small to evaluate potential publication bias.

Efficacy of APP

Is APP more efficacious than APM in terms of clinically relevant response (i.e., ≥ 25% reduction) on PANSS outcomes?

Overall

The weighted aggregated data of seven included datasets revealed that 38% of patients on APP and 30% on APM met the criterion for a clinically relevant response on the PANSS total score. There was no statistically significant difference between the two groups (odds ratio [OR]=1.37 for APP versus APM, 95% confidence interval [CI] 0.80; 2.33, p=0.199).

Aim and study population	Psycho-pathology outcome scales	Other scales	Conclusion
Conversion to clozapine monotherapy in inpatients with schizophrenia treated with clozapine-olanzapine combination.	CGI-S, CGI-I	GAF	The clinical state of patients who were on OLA + CLOZ therapy was not affected by discontinuation of olanzapine.

Study-level characteristics

There were insufficient studies per characteristic to draw any robust conclusions about possible interactions between study-level characteristics (study aim, study region or stage of illness) and treatment group on response to APP.

Patient-level characteristics

The odds of a response to APP versus APM on the PANSS total outcome increased by 41% per 10-point increase in baseline PANSS total score (OR=1.41, 95% CI 1.02; 1.94, *p*=0.037), which appeared robust in sensitivity analyses. The odds of a response to APP on the PANSS positive symptom subscale outcome doubled per 5-point increase in baseline PANSS positive symptom subscale score (OR=2.02, 95% CI 1.30; 3.12, *p*=0.002). The odds of response to APP on the PANSS negative symptom subscale outcome increased by 45% per 10-point increase in baseline PANSS total score (OR=1.45, 95% CI 1.04; 2.02, *p*=0.03). Response was not notably moderated by any of the other investigated characteristics. There was no significantly beneficial effect for any of the investigated antipsychotic combinations on response.

For an overview of the results on response see Figure 2a.

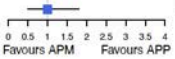
Is APP more efficacious than APM in terms of change on PANSS or CGI?

Overall

Overall, there was no significant difference in mean change on PANSS total score between the two groups (mean difference [MD]=-1.08 for APP versus APM, 95% CI -5.69; 3.53, *p*=0.596).

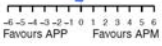
Figure 2 Forest plots representing interaction of moderators for efficacy and tolerability of APP compared with APM on PANSS total, PANSS positive and negative subscales, CGI, and SAS outcomes

Outcome	Moderator		k APP	k APM	n APP	n APM	OR (95% CI)	P-value
PANSS Total	None		7	7	211	313	1.37 [0.80; 2.33]	
	Aim study	Therapy-resistance	6	6	202	304	1.08 [0.43; 2.72]	
		Adverse effects	1	1	9	9	3.35 [0.11; 105.02]	
		Conversion monotherapy	0	0			n/a	
	APP with clozapine	Cloz. + FGA vs. cloz.	2	6#	16	102	0.18 [0.02; 1.90]	0.154
		Cloz. + SGA vs. cloz.	4	6#	85	102	1.02 [0.38; 2.73]	0.970
	APP with SGA	SGA + FGA vs. SGA	0	0			n/a	
		SGA + SGA vs. SGA	1	1	110	211	1.55 [0.97; 2.47]	0.064
	Gender	Female vs. male	7	7	211	313	1.16 [0.48; 2.78]	0.737
	Age	Per 5 years	7	7	210	312	1.00 [0.84; 1.19]	0.992
	Illness duration	Per 5 years	4	4	150	226	1.26 [0.98; 1.61]	0.070
	Illness severity at baseline	PANSS total (per 10 pts)	7	7	211	313	1.41 [1.02; 1.94]	0.037*
		PANSS positive (per 5 pts)	7	7	211	313	1.57 [1.00; 2.49]	0.052
		PANSS negative (per 5 pts)	7	7	211	312	1.27 [0.90; 1.78]	0.175
	Setting	Inpatient vs. outpatient	6	6	200	300	2.87 [0.72; 11.47]	0.136
PANSS Positive	None		8	8	225	327	1.23 [0.78; 1.95]	0.319
	Illness duration	Per 5 years	5	5	164	240	1.28 [1.00; 1.65]	0.055
	Illness severity at baseline	PANSS total (per 10 pts)	8	8	225	327	1.27 [0.94; 1.72]	0.125
		PANSS positive (per 5 pts)	8	8	225	327	2.02 [1.30; 3.12]	0.002*
PANSS Negative	None		8	8	225	326	1.00 [0.55; 1.82]	0.997
	Illness severity at baseline	PANSS total (per 10 pts)	8	8	225	326	1.45 [1.04; 2.02]	0.031*
		PANSS negative (per 5 pts)	8	8	225	326	1.26 [0.89; 1.77]	0.192
CGI-I	None		5	5	136	221	1.00 [0.50; 1.80]	0.840

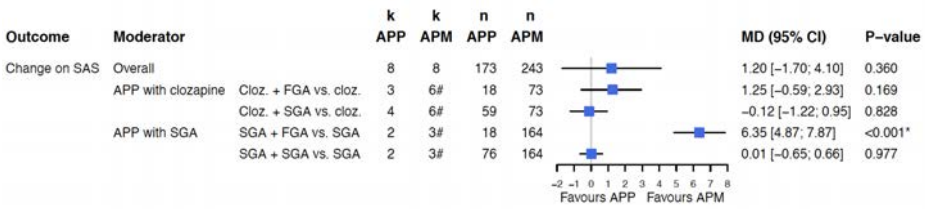


2a. Main moderators for response (i.e., ≥ 25% improvement on PANSS, or at least minimally improvement on CGI-I)

Outcome	Moderator		k APP	k APM	n APP	n APM	MD (95% CI)	P-value
Change on PANSS Total	None		8	8	228	331	−1.08 [−5.69; 3.53]	0.596
	Illness severity at baseline	PANSS total (per 10 pts)	8	8	228	331	−2.10 [−3.99; −0.20]	0.031*
		PANSS positive (per 5 pts)	8	8	228	331	−2.77 [−5.45; −0.09]	0.043*
		PANSS negative (per 5 pts)	7	7	211	312	−0.82 [−3.12; 1.48]	0.483
Change on PANSS Positive	None		9	9	242	345	−0.50 [−1.90; 0.80]	0.410
	Illness severity at baseline	PANSS total (per 10 pts)	9	9	242	345	−0.66 [−1.28; −0.04]	0.038*
		PANSS positive (per 5 pts)	9	9	242	345	−1.21 [−2.10; −0.32]	0.008*
Change on PANSS Negative	None		8	8	225	326	0.70 [−0.90; 2.40]	0.310
	APP with clozapine	Cloz. + FGA vs. cloz.	2	6#	16	101	1.75 [−0.26; 3.72]	0.092
		Cloz. + SGA vs. cloz.	4	6#	85	101	−0.24 [−1.24; 0.78]	0.643
	APP with SGA	SGA + FGA vs. SGA	1	2#	14	225	2.51 [−0.90; 5.93]	0.139
		SGA + SGA vs. SGA	1	2#	110	225	−1.25 [−2.42; −0.24]	0.027*
Change on CGI-S	None		9	9	278	192	−0.10 [−0.30; −0.10]	0.280
	Illness severity at baseline	PANSS total (per 10 pts)	8	8	187	271	−0.14 [−0.27; −0.01]	0.041*



2b. Main moderators for change from baseline on PANSS and CGI-S



2c. Main moderators for extrapyramidal side effects on SAS

Legend: APM=antipsychotic monotherapy, APP=antipsychotic polypharmacy, CGI-I=Clinical Global Impressions Improvement scale, CGI-S=Clinical Global Impressions Severity scale, CI=confidence interval, Cloz.=clozapine, FGA=first generation antipsychotic, k=number of datasets, MD=mean difference, n=number of patients, OR=odds ratio, PANSS=Positive and Negative Syndrome Scale, SAS=Simpson-Angus extrapyramidal side effects Scale, SGA=second generation antipsychotic.

*=p value <0.05

#=the number of studies in APP and APM group is not equal in the analyses of combinations of antipsychotics. This is because the placebo condition included patients from the APM group of the combination study in question, as well as patients from the APM group of other combination studies.

Study-level characteristics

There were insufficient studies per characteristic to draw any robust conclusions about a possible interaction between study-level characteristics and treatment group on change on the PANSS scores, or on the CGI.

Patient-level characteristics

Reduction of the PANSS total outcome score was significantly greater for APP versus APM in patients with higher baseline PANSS total scores (MD=-0.21, 95% CI -3.99; -0.20, *p*=0.031 per 10-point increase on baseline PANSS total score). Reduction of the PANSS total outcome score was also significantly greater for APP versus APM in patients with higher baseline PANSS positive symptom subscale scores (MD=2.77, 95% CI -5.45; -0.09, *p*=0.043 per 5-point increase on baseline PANSS positive subscale score). In sensitivity analyses, both interactions were no longer significant.

Reduction of the PANSS positive symptom subscale outcome score was significantly greater for APP versus APM, both in patients with higher baseline PANSS total scores (MD=-0.66, 95% CI -1.28; -0.004, *p*=0.038 per 10 points increase in baseline PANSS total score) and in patients with higher baseline PANSS positive symptom subscale scores (MD=-1.21, 95% CI 2.10; -0.32, *p*=0.008 per 5-point increase in baseline PANSS positive subscale score), but not in patients with higher baseline PANSS negative symptom subscale scores. These findings appeared robust in sensitivity analyses.

Reduction of the PANSS negative symptom subscale outcome score was significantly greater with combinations of two SGAs (MD=-1.25, 95% CI -2.42; -0.24, p=0.027), but was not significantly moderated by any of the other investigated characteristics.

Reduction of the CGI-S outcome score was also significantly greater for patients with higher baseline PANSS total scores (MD=-0.14, 95% CI -0.27; -0.01, *p*=0.041 per 10-point increase in baseline PANSS total score), which appeared robust in sensitivity analyses. There were no notable interactions between any of the investigated characteristics on treatment outcome on the CGI-I.

For an overview of the results on change from baseline, see the forest plot in Figure 2b.

For both APP and APM, the association between baseline illness severity on PANSS total score and the probability of respectively response and change from baseline on the PANSS total outcome score is visualized in Figure 3. We found similar results for the standardized differences of means. For the forest plots of all the investigated effect moderators, see supplementary Figures S1a – d.

Tolerability and other secondary outcomes

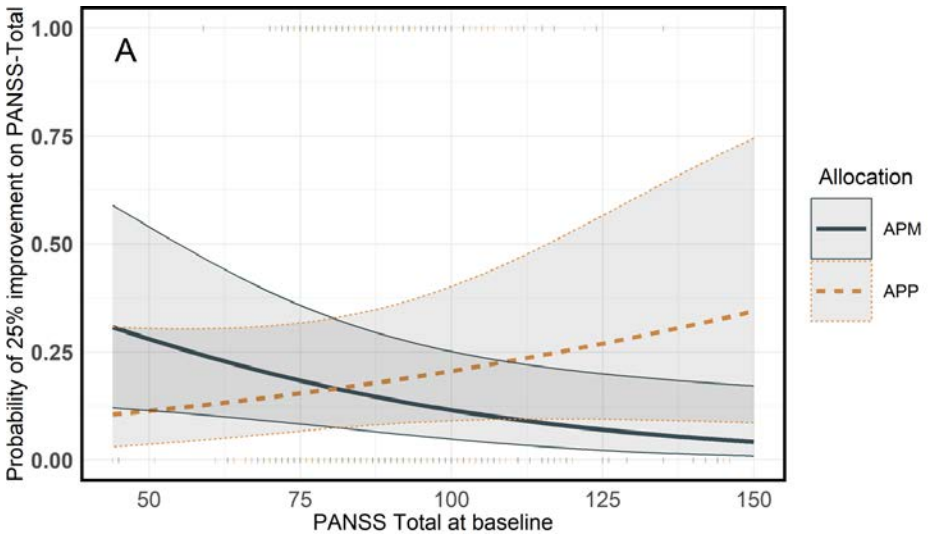
Tolerability measured with the SAS

There was no overall difference between the two groups in EPS, determined with the SAS. However, EPS were significantly more frequent with FGA-SGA combinations (MD=6.35, 95% CI 4.87; 7.87, *p*<0.001). None of the other investigated moderators interacted significantly with treatment on the SAS. For an overview, see Figure 2c.

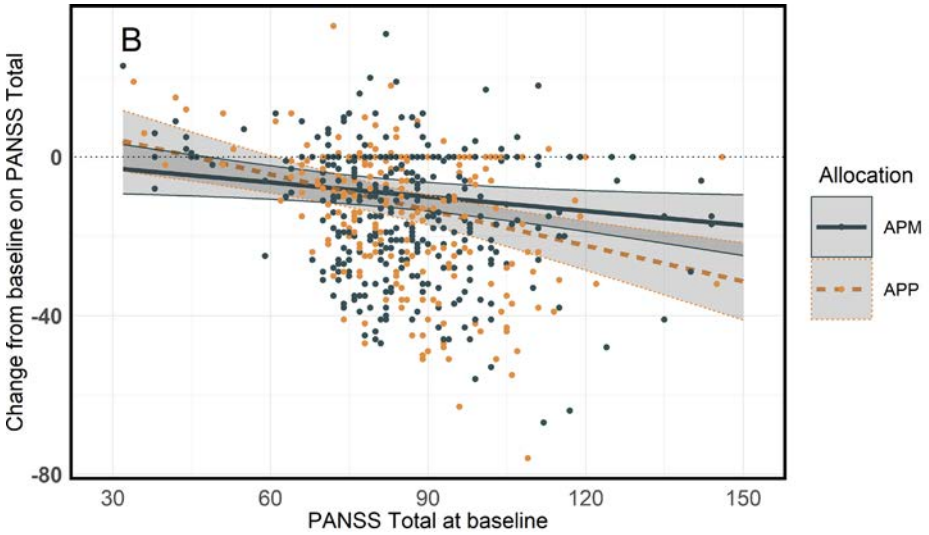
Tolerability measured with the AIMS, BARS and study discontinuation

The descriptive results of study discontinuation and adverse effects outcome scales available applied in at least four datasets; these are presented in Table 2. Discontinuation in the APP group (21%) was lower than in the APM group (28%). Outcomes on the AIMS and BARS scores were in the lower range in both groups. Due to limited/lacking data we cannot report results for cognition, residual mood symptoms, quality of life, and cost outcomes.

Figure 3: Association between the level of baseline PANSS total score and the predicted PANSS total outcome



3a. Probability of ≥ 25% improvement on PANSS total outcome



3b. Probability of change from baseline on PANSS total outcome

Legend: APM=antipsychotic monotherapy, APP=antipsychotic polypharmacy, PANSS= Positive and Negative Syndrome Scale.

Table 2 Descriptive statistics of secondary outcomes reported in ≥ 4 IPD

	APP		APM	
Variable	**Frequency (%)**		**Frequency (%)**	
All-cause discontinuation (k=10, n=599)	52 (21.1%)		99 (28.1%)	
Variable	**Baseline (SD)**	**Change from baseline (SD)**	**Baseline (SD)**	**Change from baseline (SD)**
Adverse effects				
- AIMS (range: 0 – 28) (k = 5; n=97)	1.33 (2.60)	0.18 (1.09)	1.69 (3.67)	0.11 (1.42)
- BARS (range: 0 – 9) (k = 4; n=130)	0.69 (1.15)	0.17 (0.92)	1.03 (1.73)	0.28 (2.29)

Legend: AIMS = Abnormal Involuntary Movement Scale, APM = antipsychotic monotherapy, APP = antipsychotic polypharmacy, BARS = Barnes Akathisia Rating Scale, IPD = individual patient data, k = number of patient data sets, n = number of participants, SD = standard deviation.

Discussion

We analyzed IPD on 599 patients, derived from 10 studies that were published before September 1, 2022, representing 32% of all eligible studies and 31% of all eligible patients. We found that for patients with higher baseline PANSS total scores, the odds to achieve response on the PANSS total outcome score were significantly higher for those receiving APP rather than APM. Analysis of the PANSS subscales outcomes revealed that this effect was more attributable to improvement in positive than in negative symptoms. The probability of a superior response to APP increased in patients with baseline PANSS total scores (range: 30–210) in the higher levels (in this sample approximately above 110): with every 10-point increase in baseline PANSS total score, the superiority of APP increased with approximately 2 points more reduction in PANSS total outcome score after 3–12 weeks. We could not identify specific combinations of antipsychotic medications that were more effective in reducing PANSS total or positive symptoms subscale outcome scores. Regarding the reduction of negative symptoms, combinations of two SGAs were superior to combinations involving an FGA and/or clozapine. None of the other investigated characteristics were associated with a better outcome for APP.

Pharmacotherapy with antipsychotic medication is an important cornerstone in the treatment of patients with psychotic disorders. In the absence of sufficiently explanatory etiological or neurobiological models for psychosis, the classical hypothesis is that antipsychotics reduce postsynaptic dopamine transmission in the mesolimbic area of the brain by blocking the dopamine D_2 receptor. However, at therapeutic doses, an optimum of 65% D_2 receptor blocking for maximum antipsychotic effect is reached,

implicating that a higher antipsychotic load targeting D_2 receptors will not result in greater efficacy (Kapur et al., 2000). Clozapine has superior antipsychotic efficacy in treating patients with refractory psychotic symptoms and has a complex receptor profile with only low affinity for the D2 receptor, suggesting that other receptors may play an essential role in efficacy of antipsychotics on positive and negative symptoms, such as modulation of the D_3 and serotonergic receptors (Hjorth, 2021). Combining antipsychotic medications with different receptor profiles may to some extent explain any superiority of APP, although it cannot explain the difference in efficacy we found between more and less severely psychotic patients.

A better response on APP compared with APM in those patients with a more severe psychotic illness is consistent with a previous meta-analysis where the addition of a partial D_2 agonist to a full antagonist was associated with superiority of APP versus APM in open-label and low-quality (however, not in double blind randomized controlled) trials (Galling et al., 2017). This finding cannot be explained by 'regression to the mean', since we included only placebo-controlled RCTs with balanced baseline illness severity in both treatment groups. Our finding that APP is beneficial for the most severely ill patients is also consistent with studies that have found discontinuation of APP to be less successful in more chronically and severely ill patients (Constantine et al., 2015; Borlido et al., 2016).

Our finding of a beneficial effect of combined SGAs on negative symptoms may be in line with previous findings that augmentation of D_2 antagonists with a partial D_2 agonist was associated with significantly reduced negative symptoms (Galling et al., 2017). Our study did not allow to identify specific effective combinations.

A reduction of 25% in the PANSS total score reflects a reduction of the CGI-S by one severity step while a 15-point reduction in the PANSS total score approximately corresponds to minimal improvement on the CGI-I and a change on the CGI-S by one point (Leucht et al., 2006). Thus, the magnitude of the effect in our sample was modest. Efficacy was observed with the PANSS and the CGI-S, but not with the CGI-I scale. Clinically this implies that APP treatment should be carefully assessed for any added benefit, which should be weighed against the presence of and potential risk of adverse effects.

We found a significant increase in EPS in those patients treated with both an FGA and an SGA. There was no notable difference in all-cause discontinuation between both groups. Because of limited/lacking data, we could not analyze cognitive functioning, mood symptoms, quality of life, or medical health costs.

Strengths and limitations of this study

To the best of our knowledge, this is the first IPDMA to investigate the characteristics of patients with schizophrenia-spectrum disorders that might benefit from APP. A major strength of the current study is that it allowed effect moderators to be investigated with more statistical power than is possible in study-level meta-analyses. The studies included varied in their aims, and comprised patients in various stages of their illness, which enhances the generalizability of the findings.

Several limitations should be considered. First, we were only able to obtain 31% of potentially eligible IPD, which is a relatively low retrieval rate (Wang et al., 2021), and may limit the generalizability of our findings. However, our overall comparison of studies from which we could and could not obtain IPD demonstrated that the former were a representative reflection of all studies conducted in this area, which are dominated by studies investigating the efficacy of APP in patients with treatment refractory psychotic illness (67–70%), focusing mainly on combinations including clozapine (67%) (supplementary Table S8). Secondly, superiority of APP in more severely ill patients could be explained by the higher mean total antipsychotic dose in the APP group compared with the APM group (26.8 resp. 15.3 mg olanzapine equivalents). Unfortunately, the design of the relevant studies did not allow us to unravel this explanation, which would call for differently designed studies with increasing doses in the monotherapy arm (Azorin and Simon, 2020). However, a previous systematic review did not find any therapeutic advantage for higher antipsychotic dosing (Samara et al., 2018). Thirdly, the included studies represented only a proportion of the possible antipsychotic combinations and were analyzed in broad categories (FGA, SGA, and clozapine combinations), impairing robust conclusions about the effectiveness of specific combinations of antipsychotic medications in particular patient subgroups.

Conclusions

The efficacy of APP versus APM in patients with schizophrenia-spectrum disorders depends on the severity of the disorder: APP is more effective for patients with high PANSS total scores, driven mostly by the positive symptoms. In those with less severe refractory illness and predominantly negative symptoms, APP appears to be no more effective than APM. Any incremental benefit for APP versus APM was modest and should be individually weighed against side-effect burden, especially when combining an FGA with an SGA. The findings of this meta-analysis may be helpful in the future revision of guidelines and for those clinicians making treatment

decisions for severely ill patients with schizophrenia-spectrum disorders. More research is needed to identify which combinations of antipsychotics are favorable, and to determine the impact of APP on important non-psychopathological parameters, like functional outcome, quality of life, and cost-effectiveness.

Declaration of competing interest

Dr. Anıl Yağcıoğlu has received speaker/advisory board fees Janssen, Abdi İbrahim Otsuka and Nobel, and has received investigator fees from Janssen. Dr. Kasper served in the past 3 years as a consultant or on advisory boards for Angelini, Biogen, Boehringer, Esai, Janssen, IQVIA, Mylan, Recordati, Rovi, Sage and Schwabe; and he has served on speakers bureaus for Angelini, Aspen Farmaceutica S.A., Biogen, Janssen, Recordati, Schwabe, Servier, Sothema, and Sun Pharma. Dr. R.E. Nielsen has received funding for research or has been an investigator for H. Lundbeck, Otsuka Pharmaceuticals, Compass, Boehringer Ingelheim and Janssen-Cilag. Furthermore, REN has received speakers fee from Bristol-Meyers Squibb, Astra Zeneca, Janssen-Cilag, Lundbeck, Servier, Otsuka Pharmaceuticals, Teva and Eli Lilly. Dr. Remington has received research support from the Canadian Institutes of Health Research (CIHR), University of Toronto, and HLS Therapeutics Inc. Dr. Schmidt-Kaepelin is patent holder of patent No.: 102020106962, and has received speakers honoraria by Boehringer Ingelheim. Dr. Correll has been a consultant and/or advisor to or has received honoraria from: AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Biogen, Boehringer-Ingelheim, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Denovo, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Jamjoom Pharma, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Merck, Mindpax, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Neurelis, Newron, Noven, Novo Nordisk, Otsuka, Pharmabrain, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Sage, Seqirus, SK Life Science, Sumitomo Pharma America, Sunovion, Sun Pharma, Supernus, Takeda, Teva, Tolmar, Vertex, and Viatris. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Compass Pathways, Denovo, Lundbeck, Relmada, Reviva, Rovi, Supernus, and Teva. He has received grant support from Janssen and Takeda. He received royalties from UpToDate and is also a stock option holder of Cardio Diagnostics, Kuleon Biosciences, LB Pharma, Mindpax, and Quantic. Lochmann van Bennekom, IntHout, Gijsman, Akdede, Barnes, Galling, Gueorguieva, Kreinin, J. Nielsen, Repo-Tiihonen, Shafti, Xiao and Verkes reported no conflicts of interest.

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Supplemental Material

Efficacy and Tolerability of Antipsychotic Polypharmacy for Schizophrenia-Spectrum Disorders.

A Systematic Review and Meta-Analysis of Individual Patient Data

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Schizophr Res. 2024 Oct;272:1-11.

List of Supplemental Material

Table S1 Search String

Sources	Search String
PubMed, EMBASE, and Cochrane Central Register of Randomized trials.	(schizophrenic OR schizophrenia OR "schizophreniform disorder" OR schizoaffective OR schizo-affective OR "psychotic disorder") AND (antipsychot* OR neuroleptic* OR amisulpride OR asenapine OR aripiprazole OR chlorpromazine OR chlorprotixene OR clozapine OR droperidol OR flupentixol OR fluphenazine OR flusperilene OR haloperidol OR levomepromazine OR loxapine OR lurasidone OR olanzapine OR paliperidone OR pimozide OR quetiapine OR reserpine OR risperidone OR sulpiride OR thioridazine OR thiothixene OR trifluoperazine OR ziprasidone OR zotepine OR zuclopentixol) AND (polypharmacy OR polytherapy OR combination OR co-administration OR augmentation* OR add-on OR addition* OR supplement* OR cotreatment OR co-treatment OR co-prescription OR coprescription OR adjunctive* OR concurrent* OR concomitant* OR simultaneous* OR combined*) AND (random* OR placebo)

Methods S1 Data extraction

From the obtained individual patient data (IPD) we extracted clinical data (gender, age, ethnicity, diagnosis, duration of illness, stage of illness, inpatient or outpatient status, number of hospitalizations, initial antipsychotic plus dose, additional antipsychotic plus dose, cumulative antipsychotic dose, prior clozapine treatment), trial data (year of study, region of study, aim of study [e.g., treating refractory positive/negative symptoms, treating adverse effects, conversion to antipsychotic monotherapy; APM], trial duration, primary antipsychotic agent and dose, additional antipsychotic agent and dose) and outcome measures at baseline and follow up (treatment response assessed by symptom rating scales, global assessment of functioning (GAF) scores, quality of life, cost, and adverse events). In case of a trial converting polypharmacy to monotherapy we set the continued agent as primary antipsychotic (AP) and the tapered-off agent as additional AP.

Table S2 Applied conversion formulas for standardization of outcome measures to (converted) PANSS ratings and antipsychotic doses to olanzapine dose equivalents.

Conversion	Method
SAPS composite ratings to PANSS positive subscale ratings	To calculate converted PANSS positive subscale ratings from SAPS composite ratings we used the conversion formula by van Erp et al. (van Erp et al., 2014): • Converted PANSS positive = 11.1886 + (0.2587 * SAPS [composite] total score).
SANS composite ratings to PANSS negative subscale ratings	To calculate converted PANSS negative ratings from SANS composite ratings we used the conversion formula by van Erp et al. (van Erp et al., 2014): • Converted PANSS negative = 7.1196 + (0.3362 * SANS [composite] total score).
BPRS ratings to PANSS total ratings	To calculate converted PANSS total ratings from BPRS ratings we used equipercentile linking as proposed by Leucht et al. (Leucht et al., 2013).
BPRS ratings to PANSS positive subscale ratings	To calculate converted PANSS positive ratings from BPRS ratings we extracted and added up the 7 items ratings of positive symptomatology of the BPRS (i.e., delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness, and hostility), that both in content and in rating range very highly correlate with the 7 PANSS positive items.
CGI-S	One discontinuation study (Repo-Tiihonen 2012) only applied CGI-S and CGI-I scores. We did not attempt to convert CGI-S ratings into PANSS ratings since we could not find any publication that examined a possible correlation of CGI-S ratings with PANSS ratings. Any estimate would introduce too much inaccuracy in the data.
Calculation of the cumulative antipsychotic dose	To compare mean antipsychotic doses between APP and APM conditions across studies, we recalculated the final (cumulative) antipsychotic dose in olanzapine dose equivalents using the concept of the Defined Daily Dose (DDD) of the World Health Organisation (http://www.whocc.no/), applying the antipsychotic dose conversion website tool by Leucht et al. (https://view.officeapps.live.com/op/view.aspx?src=http%3A%2F%2Fwww.cfdm.de%2Fmedia%2Fdoc%2FAntipsychotic%2520dose%2520conversion%2520website.xls&wdOrigin=BROWSELINK). Although DDD's were not developed to measure dose equivalence, they are a feasible estimate of the total antipsychotic load because they are internationally accepted measures based on reviews of various sources and are available for almost all antipsychotic drugs (Leucht et al., 2016).

Methods S2 Adaptation in statistical analyses plan for primary and secondary outcome measures

For reasons of completeness, in the original study design as registered in PROSPERO, we had included a large number of primary and secondary outcome measures:

Primary outcomes
Change in total psychopathology, positive symptoms, negative symptoms, and global illness severity, as well as study defined response status, either based on a percentage change from baseline, or much or very much improved on the CGI-I, each from baseline to endpoint

Secondary outcomes
All-cause discontinuation, discontinuation due to inefficacy, discontinuation due to intolerability, study-defined remission, adverse effect frequency and severity, cognition, depression severity, quality of life, and cost.

Before performing the analyses, we decided to restrict the primary outcome measure to a clinically relevant response, defined as at least 25% reduction in PANSS total outcome, which is scientifically and clinically a very pertinent outcome. Outcomes on improvement on the CGI-I scale, change on the PANSS total, positive and negative subscales, and CGI-S scale were defined as secondary outcomes, as described in the paper. Due to insufficient information, we could not perform planned *per protocol* analyses. *As treated* analyses were equal to the intention-to-treat analyses. As also described in the main paper, due to limited or lacking data, we could not report on outcomes for cognition, mood symptoms, quality of life, and costs.

Methods S3 Statistical analyses

Using R version 4.2.2 (R Core Team, 2022) with RStudio (RStudio Team, 2022), we examined the relationship between each potential moderator and outcome. In the analyses of the binary outcomes (response yes/no) we excluded the discontinuation studies, as the definition of a positive response, i.e., a decrease in PANSS, in a discontinuation study is not to be expected. This problem is not applicable for the continuous outcomes, where also increases in PANSS scores can be included in the analyses.

Effects of study-level characteristics (e.g., study aim) were analyzed with a two-stage approach. First, per outcome, the differences between APP and APM were estimated for each study using a (generalized) linear model, and pooled in a random-effects meta-analysis, using the Mantal Haenszel method (exact =false), a REML estimator for the heterogeneity parameter τ^2, and the Hartung-Knapp-Sidik-Jonkman (IntHout et al., 2014) (HKSJ) adjustment. Next, we updated the meta-analysis models with the potential modifier, where we assumed a common τ^2 across the subgroups, resulting in subgroup analyses. For this, we used the R package meta version 6.2-1 (Balduzzi et al., 2019), with outcome measure odds ratio for binary outcomes and mean difference for change from baseline outcomes, and in addition for the PANSS total and positive and negative subscales the bias corrected standardized mean difference (SMD, Hedges' g) (Hedges, 1981).

Effects of participant level characteristics were analyzed in a one-stage approach. We started with descriptive statistics and plots per study showing the individual (0/1) responses or change from baseline values versus the original moderator values, in combination with the predicted response per treatment based on either a nonlinear or a logistic/linear regression model per study. We evaluated nonlinearity of the patterns per study, using a thin plate regression spline basis with a thin plate (smoothing) spline penalty per treatment group and study, in the studies with enough variation in modifier-values, however these figures were in general less informative than the logistic/linear regression models per study. For the smoothing splines we used the R package mgcv version 1.8-41 (Wood, 2003; Wood, 2011; Wood, 2017). Further, we made descriptive statistics per study and treatment group, comparing baseline moderator values.

After these initial steps to explore patterns across studies, we first evaluated with smoothing splines in mixed (generalized) additive linear models whether a linear or a nonlinear relation was preferred between the moderator and the outcome. We started with a (generalized) additive model (GAM) with as dependent variable the outcome, for example 25% improvement in PANSS total score, or change from baseline in PANSS total score. We added as fixed effects the treatment group (as factor variable), the potential moderator, the interaction of the moderator with the treatment group, and the baseline variable of the continuous version of the dependent variable (in this example: baseline PANSS total score). We added random effects for the intercept, treatment, and moderator per study. In case of a binomial outcome, we used a binomial distribution with a logit link (as a log link, which would result in risk ratio's, often did not converge). Models were fitted with maximum likelihood (ML). To decide whether the nonlinearity was improving the

model fit, we compared the Akaike Information Criterion (AIC) values (Akaike, 1973) of the models with and without the smoothing splines and checked the p-value for the likelihood ratio test of the model comparison. If the AIC values were similar (e.g., at most 2 points difference), and the p-value of the LR test was >0.05, we chose the simpler model, i.e., the mixed logistic/linear regression model without added splines. This appeared to be the case for all moderator-outcome combinations.

Based on the resulting model, where we could thus use a linear predictor, we replaced the original moderator with the centered moderator, i.e., with study-centered and study-mean values, and we focused on the estimate of the coefficient for the interaction between the centered moderator and treatment, in order to estimate within-study treatment effect modification, using restricted maximum likelihood (REML) for estimation.

We conducted the following sensitivity analyses:
- Removing the patients with the lowest or highest 1% moderator values.
- Removal of the discontinuation studies
- Ad hoc sensitivity analyses, e.g., without a certain study if we mistrusted the regression results of a particular study.

For the PANSS total, positive subscale and negative subscale scores we also conducted the one-stage analyses with standardized change from baseline values. We calculated per study the pooled standard deviation, using Hedges' formula (Hedges, 1981):

$$SD_{pooled} = sqrt(((n_1-1)*SD_1\text{^}2 + (n_2-1)*SD_2\text{^}2) / (n_1+n_2-2)),$$

and divided the individual changes from baseline by the pooled SD of the applicable study, after which we conducted the one-stage analyses as described above.

Graphical representations of the results were made with the R package ggplot2 version 3.4.2 (Wickham, 2016). To translate the results of the centered analyses, we compared models with and without a centered moderator, and when these were very similar, we visualised the results of the non-centered moderator. On the y-axis we showed the predicted response or change from baseline value for a person with a median value for the baseline variable (e.g., 85 for baseline PANSS total score). In the forest plots showing all interaction terms, we show the results of the centered analyses.

Table S3 Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data (PRISMA-IPD) (Stewart et al., 2015) checklist of items to include when reporting a systematic review and meta-analysis of individual participant data

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	Title page
Abstract			
Structured summary	2	Provide a structured summary including as applicable: **Background**: state research question and main objectives, with information on participants, interventions, comparators and outcomes. **Methods**: report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias. **Results**: provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice. **Discussion:** state main strengths and limitations of the evidence, general interpretation of the results and any important implications. **Other:** report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	Abstract
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	§ 1
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	§ 1
Methods			
Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	§ 2.1
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	§ 2.2

Table S3 Continued

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Identifying studies - information sources	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	§ 2.3
Identifying studies - search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table S1.
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	§ 2.3
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study).	§ 2.4, Methods S1
		If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardising or translating variables within the IPD datasets to ensure common scales or measurements across studies.	§ 2.4, Methods S1, Table S2
IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	§ 2.5
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	§ 2.5
Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	§ 2.6

Table S3 Continued

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Synthesis methods	14	Describe the meta-analysis methods used to synthesise IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): • Use of a one-stage or two-stage approach. • How effect estimates were generated separately within each study and combined across studies (where applicable). • Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for. • Use of fixed or random effects models and any other model assumptions, such as proportional hazards. • How (summary) survival curves were generated (where applicable). • Methods for quantifying statistical heterogeneity (such as I^2 and τ^2). • How studies providing IPD and not providing IPD were analysed together (where applicable). • How missing data within the IPD were dealt with (where applicable).	§ 2.6, Methods S2+ Methods S3
Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified.	§ 2.6, Methods S3
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	Table S6 + table S7
Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	§ 2.6
Results			
Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	Figure 1
Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	Table 1
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	§ 3.2
Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	§ 3.2, Table S6

Table S3 Continued

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot.	Figure 2, Figure S1
Results of syntheses	21	Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.	Figure 2
		When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.	
		Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.	
Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	§ 3.1, § 4
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarise the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	§ 3.3, 3.4, Figure 2
Discussion			
Summary of evidence	24	Summarise the main findings, including the strength of evidence for each main outcome.	§ 4
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	§ 4
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	§ 4
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	§ 5
Funding			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	§ 6

Table S4 GRADE (Atkins et al., 2004) rating of statistically significant moderators

GRADE Summary of Outcomes. Assessment of certainty of main moderators for efficacy and tolerability of APP vs. APM

Patients: adult patients with schizoprenia spectrum disorders
Intervention: APP
Comparison: APM
Outcome for efficacy: response on PANSS total and CGI-I, change on PANSS total and CGI-S.
Outcome for tolerability: change on SAS

Effect modifier	Certainty assessment					
	No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision
	Outcome on response, i.e. ≥ 25% reduction on the PANSS total outcome score					
Illness severity: baseline PANSS total score	7	Randomised controlled trials	Not serious 3 low (n=419), 1 some concerns (n=50), 3 high (n=55)	Serious	Some Indirectness (discontinuation studies, adverse effect studies)	Serious
	Low certainty					
Illness severity: baseline PANSS positive subscale score	8	Randomised controlled trials	Not serious 3 low (n=419), 2 some concerns (n=78), 3 high (n=55)	Serious	Some Indirectness (discontinuation studies, adverse effect studies)	Serious
	Outcome on response, i.e. ≥ 25% reduction on the PANSS negative subscale outcome score					
Illness severity: baseline PANSS total score	8	Randomised controlled trials	Not serious 3 low (n=419), 2 some concerns (n=78), 3 high (n=55)	Serious	Some Indirectness (discontinuation studies, adverse effect studies)	Serious
	Outcome on change on PANSS total outcome score					
Illness severity: baseline PANSS total score	8	Randomised controlled trials	Not serious 4 low (n=454) 1 some concerns (n=50), 3 high (n=55)	Serious	Some Indirectness (discontinuation studies, adverse effect studies)	Serious
Illness severity: baseline PANSS positive subscale score	8	Randomised controlled trials	Not serious 4 low (n=454) 1 some concerns (n=50), 3 high (n=55)	Serious	Some Indirectness (discontinuation studies, adverse effect studies)	Serious

	No of patients		Effect		Certainty	Importance
Other considerations	Intervention (APP)	Controls (APM)	Relative (95% CI)	Absolute (95% CI)		
None	211	313	OR=1.41, 95% CI 1.02; 1.94, p=0.037 per 10-point increase of baseline PANSS total score		⊗⊗○○ Low certainty	Important
None	225	327	OR=2.02, 95% CI 1.30; 3.12, p=0.002 per 5-point increase in baseline PANSS positive subcale		⊗⊗○○ Low certainty	Important
None	225	326	OR=1.45, 95% CI 1.04; 2.02, p=0.031 per 10-point increase of baseline PANSS total score		⊗⊗○○ Low certainty	Important
None	228	331		MD=-0.210, 95% CI -3.99; -0.20, p=0.031 per 10-point increase on baseline PANSS total score	⊗⊗○○ Low certainty	Important
None	228	331		MD=-2.768, 95% CI -5.45; -0.09, p=0.043 per 5-point increase on baseline PANSS positive subscale score	⊗⊗○○ Low certainty	Important

Table S4 Continued

Effect modifier	Certainty assessment					
	No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision
	Outcome on change on PANSS positive outcome score					
Illness severity: baseline PANSS total score	9	Randomised controlled trials	Not serious 4 low (n=454), 2 some concerns (n=78), 3 high (n=55)	Serios	Some Indirectness (discontinuation studies, adverse effect studies)	Serious
Illness severity: baseline PANSS positive subscale score	9	Randomised controlled trials	Not serious 4 low (n=454), 2 some concerns (n=78), 3 high (n=55)	Serious	Some Indirectness (discontinuation studies, adverse effect studies)	Serious
	Outcome on change on PANSS negative outcome score					
Combination of antipsychotics: SGA + SGA	2	Randomised controlled trials	Not serious 1 low (n=335, 1 some concerns (n=28)	Not serious	Not serious	Not serious
	Outcome on change on CGI-S outcome score					
Illness severity: baseline PANSS total score	8	Randomised controlled trials	Not serious 3 low (n=386), 2 some concerns (n=78), 3 high (n=55)	Serious	Some Indirectness (discontinuation studies, adverse effect studies)	Serious
	Outcome on change on SAS outcome score					
Combination of antipsychotics: SGA + FGA	3	Randomised controlled trials	Not serious 2 low (n=230), 1 some concerns (n=28)	Not serious	Not serious	Not serious

Legend: APM=antipsychotic monotherapy, APP=antipsychotic plypharmacy, CGI-I=clinical global impressions Improvement scale, CGI-S=Clinical Global Impressions Severity scale, CI=confedence Interval, FGA=first generation antipsychotic, MD=mean difference, OR=odds ratio, PANSS=Positive and Negative symynrome, Positive and Negative Syndrome Scale, SAS=Simpson-Angus extrapyramidal side effects Scale, SGA=second generation antipsychotic.

Imprecision:

1. If the optimal information size criterion is not met, rate down for imprecision, unless the sample size is very large (at least 2000, and perhaps 4000 patients).
2. If the OIS criterion is met and the 95% CI excludes no effect (i.e. CI around RR excludes 1.0), do not rate down for imprecision.
3. If OIS criterion is met, and the 95% CI overlaps no effect (i.e. CI includes RR of 1.0) rate down for imprecision if the CI fails to exclude important benefit or important harm. (see Example 8)

	No of patients		Effect		Certainty	Importance
Other considerations	Intervention (APP)	Controls (APM)	Relative (95% CI)	Absolute (95% CI)		
None	242	345		MD=-0.66, 95% CI -1.28; -0.004, p=0.038 per 10 points increase in baseline PANSS total score	⊗⊗◯◯ Low certainty	Important
None	242	345		MD=-1.21, 95% CI -2.10; -0.32, p=0.008 per 5-point increase in baseline PANSS positive subscale score	⊗⊗◯◯ Low certainty	Important
None	110	225		MD=-1.25, 95% CI -2.42; -0.24, p=0.027	⊗⊗⊗⊗ High certainty	Important
None	187	271		MD=-0.14, 95% CI -0.27; -0.01, p=0.041 per 10 points increase in baseline PANSS total score	⊗⊗◯◯ Low certainty	Important
None	18	164		MD=6.35, 95% CI 4.87; 7.87, p<0.001	⊗⊗⊗⊗ High certainty	Important

Table S5 Baseline characteristics of included 599 participants in the IPDMA

Variable	k	N	APP (N = 247; 41.2%)	APM (N = 352; 58.8%)
Sex Male (N, %) Female (N, %)	10	599	(N = 247) 155 (62.8%) 92 (37.2%)	(N=352) 242 (68.7%) 110 (31.3%)
Age in years Mean (range; SD)	10	597	(N = 246) 40.3 (19 – 68; 11.7)	(N = 351) 40.0 (18 – 64; 11.3)
Duration of illness in years Median (range; SD)	6	435	(N = 179) 9.8 (0 – 45; 10.0)	(N = 256) 9.9 (0 – 44; 10.0)
Initial severity at baseline on (converted) total PANSS Mean (range; SD)	7	559	(N = 228) 85.0 (34 – 146; 15.8)	(N = 331) 85.6 (32 – 190; 17.4)
Initial illness severity at baseline on CGI-S Mean (range; SD)	9	531	(N = 212) 4.9 (2 – 7; 0.9)	(N = 319) 4.9 (0 – 7; 0.9)
Stage of illness First episode (N, %) Recurrent with acute exacerbation (N, %) Chronic psychosis (N, %) Refractory (N, %)	3	379	(N = 140) -- 110 (78.6%) 14 (10.0%) 16 (11.4%)	(N = 239) -- 211 (88.3%) 14 (5.9%) 14 (5.9%)
Number of hospitalizations Median (range; SD)	4	357	(N = 135) 3.0 (0 – 26; 4.8)	(N = 222) 3.5 (0 – 40; 6.3)
Total antipsychotic end dose in mg olanzapine equivalents Mean (range; SD)	7	513	(N= 207) 26.8 (5.5 – 55.0; 10.4)	(N= 306) 15.3 (3.0 – 66.0; 7.1)

Abbreviations: APM = antipsychotic monotherapy, APP = antipsychotic polypharmacy, k = number of patient data sets, N = number of patients, SD = standard deviation

Table S6 Characteristics of eligible studies for which no IPD were received

	Study	Region	n (I/C)	Comparison	Duration	Primary aim
Clozapine combinations						
1	(Assion et al., 2008)	Europe (Germany)	16 (13/3)	CLOZ + AMI vs. CLOZ	6w	TR
2	(Chang et al., 2008)	Asia (Korea)	62 (30/32)	CLOZ + ARI vs. CLOZ	8w	TR
3	(Fan et al., 2013)	North America (US)	30 (16/14)	CLOZ + ARI vs. CLOZ	8w	AE
4	(Fleischhacker et al., 2010)	Europe + North America (Austria, Finland, France, Belgium, US)	207 (108/99)	CLOZ + ARI vs. CLOZ	16w	AE
5	(Freudenreich et al., 2007)	North America (US)	24 (11/13)	CLOZ + RIS vs. CLOZ	6w	TR
6	(Friedman et al., 2011)	North America (US)	53 (25/28)	CLOZ + PIM vs. CLOZ	12w	TR
7	(Honer et al., 2006)	Asia, North America + Europe (Canada, Germany, China, UK)	68 (34/34)	CLOZ + RIS vs. CLOZ	18w	TR
8	(Josiassen et al., 2005)	North America (US)	40 (20/20)	CLOZ + RIS vs. CLOZ	12w	TR
9	(Muscatello et al., 2011)	Europe (Italy)	40 (20/20)	CLOZ + ARI vs. CLOZ	24w	TR
10	(Muscatello et al., 2014)	Europe (Italy)	40 (20/20)	CLOZ + ZIP vs. CLOZ	16w	TR
11	(Shiloh et al., 1997)	Asia (Israel)	28 (16/12)	CLOZ + SUL vs. CLOZ	10w	TR
12	(Sulejmanpasic and Bise, 2019)	Europe (Bosnia and Herzegovina)	4 (2/2)	CLOZ + AMI vs. CLOZ	8w	TR
13	(Weiner et al., 2010)	North America (US)	69 (33/36)	CLOZ + RIS vs. CLOZ	16w	TR
14	(Yao, 1999)	Asia (China)	41 (21/20)	CLOZ + SUL vs. CLOZ	6w	TR

	Conclusion	APP > APM	Commentary
	No effect on primary outcome (BPRS), beneficial effect on secondary, global outcomes (GAF, CGI and MADRS).	No	Potentially interested, no data received
	No significant improvement on primary outcome of total symptom severity in schizophrenia, a favorable change in the negative symptom domain was observed.	No	No response
	There were no significant differences between the two groups in week 8 changes for the PANSS total score.	No	No response
	There were no significant differences in Positive and Negative Syndrome Scale total score changes between groups but CGI-I and Investigator's Assessment Questionnaire scores favoured aripiprazole over placebo.	No	No cooperation
	Our trial does not support the routine addition of risperidone to clozapine in refractory schizophrenia patients.	No	Data unavailable
	There is no suggestion from this rigorously conducted trial to suggest that pimozide is an effective augmenting agent if an optimal clozapine trial is ineffective.	No	No response
	In this short-term study, the addition of risperidone to clozapine did not improve symptoms in patients with severe schizophrenia.	No	No cooperation
	In patients with a suboptimal response to clozapine, the addition of risperidone improved overall symptoms and positive and negative symptoms of schizophrenia.	Yes	Data unavailable
	The results obtained indicate that aripiprazole added to stable clozapine treatment showed a beneficial effect on the positive and general psychopathological symptomatology in a sample of treatment-resistant schizophrenia patients.	Yes	No response
	The results obtained indicate that ziprasidone was more effective than placebo in reducing negative and general psychopathological symptoms; the overall clinical improvement during ziprasidone treatment is further highlighted by changes in BPRS total score that showed evidence of a minor but nonsignificant trend.	Yes	No response
	The clozapine-sulpiride group exhibited substantially greater and significant improvements in positive and negative psychotic symptoms.	Yes	Data unavailable
	The addition of amisulpride improved overall symptoms and positive and negative symptoms of schizophrenia.	Yes	No response
	The study results suggest that adjunctive risperidone may have a modest benefit for treatment-resistant clozapine patients.	Yes	Potentially interested, no data received
	Clozapine combination with sulpiride in the treatment of schizophrenia, particularly in the treatment of the nagative schizophrenic symptoms has a good efficacy and safety .	Yes	No response

Table S6 Continued

	Study	Region	n (I/C)	Comparison	Duration	Primary aim
Non-clozapine combinations						
15	(Chen et al., 2015) / (Chen et al., 2014)	Asia (China)	119 (30/29/30/30)	RIS + ARI vs. RIS	8w	AE
16	(Henderson et al., 2009)	North America (US)	14 (7/7 + cross over)	OLA + ARI vs. OLA	2x 4w + 2w wash-out	AE
17	(Kane et al., 2009)	North America (US)	177 (90/87) 146 (78/68)	RIS + ARI vs. RIS QUE + ARI vs. QUE	16w	TR
18	(Kelly et al., 2018)	North America (US)	46 (25/21)	FGA + ARI vs. FGA	16w	AE
19	(Liang et al., 2014)	Asia (China)	41 (20/21)	PAL + ARI vs. PAL	4w	AE
20	(Shim et al., 2007)	Asia (Korea)	54 (26/28)	HAL + ARI vs. HAL	8w	AE
21	(Yasui-Furukori et al., 2012)	Asia (Japan)	36 (18[10/8]/18)	RIS/OLA + ARI vs. RIS/OLA	12w	TR

Abbreviations: AE=adverse event, AMI=amisulpride, ARI=aripiprazole, CLOZ=clozapine, Dur.=trial duration, FGA=first generation antipsychotic, HAL=haloperidol, n (I/C)=total number of patient (number allocated to intervention group/number allocated to control group), OLA=olanzapine, PAL=paliperidone, PIM=pimozide, QUE=quetiapine, RIS=risperidone, SUL=sulpiride, TR=treatment resistant psychotic symptoms, ZIP=ziprasidone.

	Conclusion	APP > APM	Commentary
	No significant changes were observed in any treatment groups regarding psychopathology and adverse effect ratings.	No	No response
	There was no significant change in total PANSS total or subscores.	No	No response
	The addition of aripiprazole to risperidone or quetiapine was not associated with improvement in psychiatric symptoms.	No	Data unavailable
	There were no significant treatment group differences in BPRS, SANS, or CGI scores	No	No data sharing
	The prolactin changes of the two groups after the treatment had no significant correlation with the scores of PANSS and its subscales ($P > 0.05$).	No	No response
	Adjunctive aripiprazole treatment reversed hyperprolactinemia in both sexes, resulting in reinstatement of menstruation in female patients, with no significant effects on psychopathology and extrapyramidal symptoms.	No	Potentially interested, no data received
	In a primary analyses, ANCOVA showed that there was an interaction between the treatment group and time for verbal fluency ($p < 0.05$), but not for any domain in BACS, PANSS or UKU side effect rating scales. Upon secondary analysis, however, the ameliorative change in motor speed as assessed by the BACS ($p < 0.05$) for those receiving aripiprazole was greater than that for the placebo group, whereas deterioration in verbal fluency ($p < 0.01$) and executive function ($p < 0.01$) in those receiving aripiprazole was significantly greater than in the placebo group.	No	Potentially interested, no data received

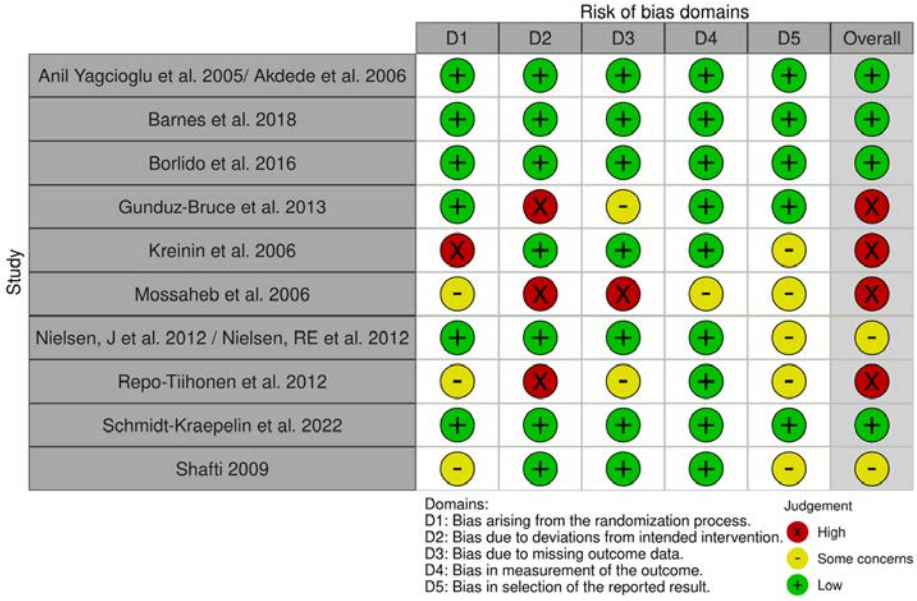
Table S7 Comparison of the characteristics of the studies from which we could and could not obtain IPD (N=21, n=1957)

	Eligible studies of which IPD was obtained	Eligible studies of which IPD was not obtained
Studies	10 (32%)	21 (68%)
Publication years	2005 – 2022	1997 – 2019
Participants APP / APM	602 (31%) 248 (41%) / 354 (59%)	1355 (69%) 663 (49%) / 692 (51%)
Study region • Asia • Europe • North America	3 (30%) 5 (50%) 2 (20%)	8* (33%) 6* (25%) 10* (42%)
Aim of study • Refractory psych. • Side effects • Discontinuation APP	7 (70%) 1 (10%) 2 (20%)	14 (67%) 7 (33%) 0 (0%)
Comparison • Clozapine combinations • Non-clozapine combinations	7 (70%) (AMI, HAL, OLA, PIM, RIS, SER) 3 (30%) (OLA+AMI, OLA+FLU-dec, mixed AP combinations)	14 (67%) (AMI, ARI, RIS, PIM, SUL, ZIP) 7 (33%) (FGA+ARI, HAL+ARI, OLA+ARI, PAL+ARI, RIS+ARI, QUE+ARI, RIS/OLA+ARI)
Outcome efficacy APP > APM	3/10 (30%)	7/21 (33%)

* Sum of studies is >21 because 1 study was performed in both Europe and North America, and 1 study was performed in Asia, Europe, and North America.

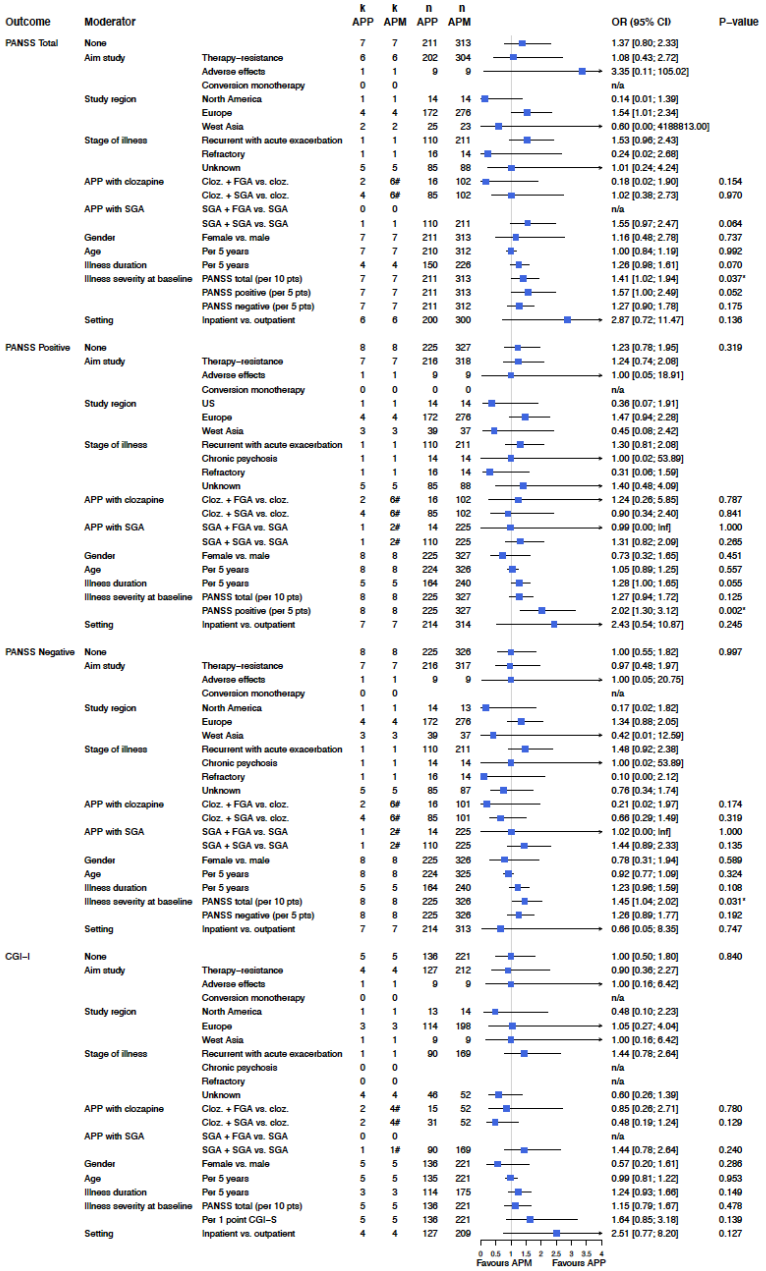
Abbreviations: APP=antipsychotic polypharmacy, APM=antipsychotic monotherapy, AP=antipsychotic, AMI=amisulpride, ARI=aripiprazole, FGA=first generation antipsychotic, FLU-dec=fluphenazine decanoate, HAL=haloperidol, OLA=olanzapine, PIM=pimozide, QUE=quetiapine, RIS=risperidone, SER=sertindole, SUL=sulpiride.

Table S8 Risk of bias assessment of individual studies according to the Cochrane Risk of Bias 2 Tool (RoB 2 tool)

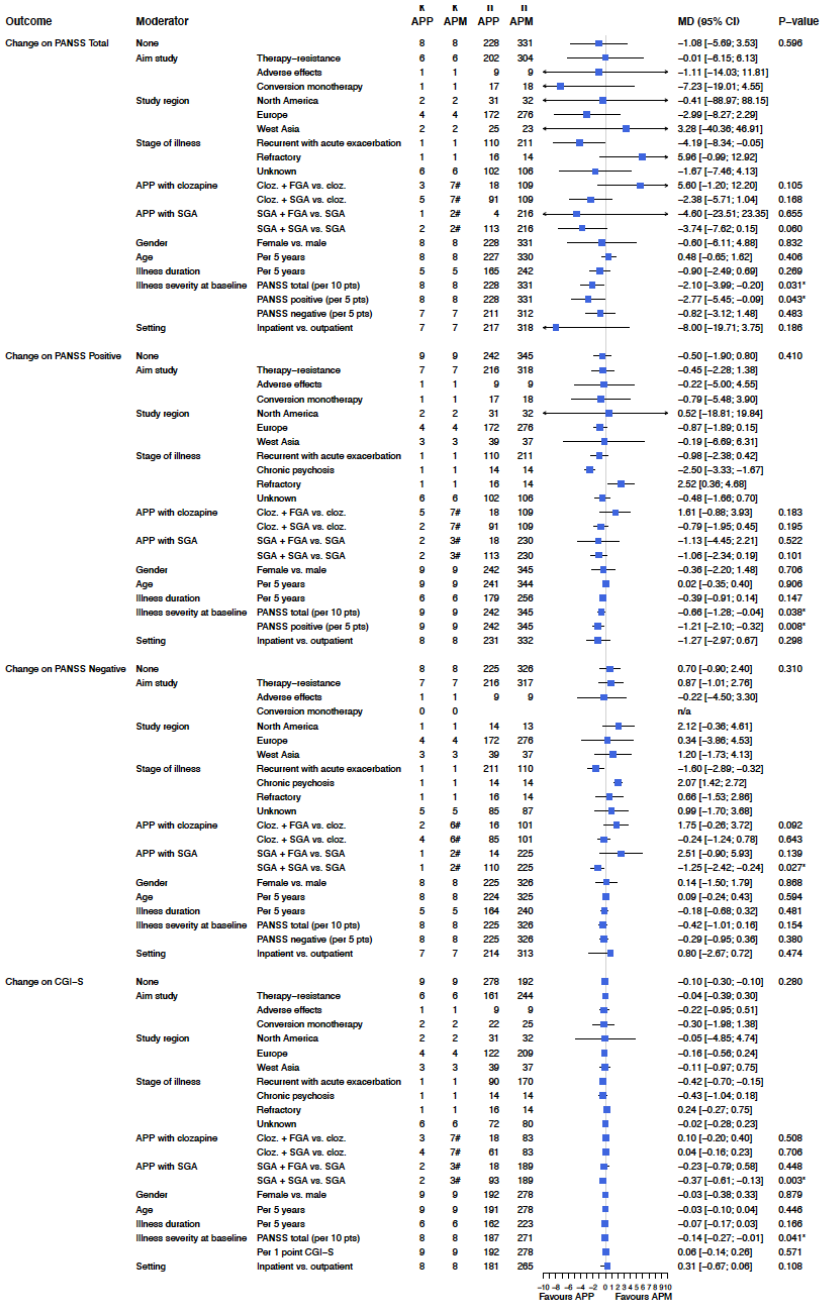


Created by Robvis (McGuinness and Higgins, 2021)

Figure S1 Comprehensive forest plots summarizing all investigated moderators for efficacy and tolerability of APP compared to APM on PANSS total, PANSS positive and negative subscales, CGI, and SAS outcomes

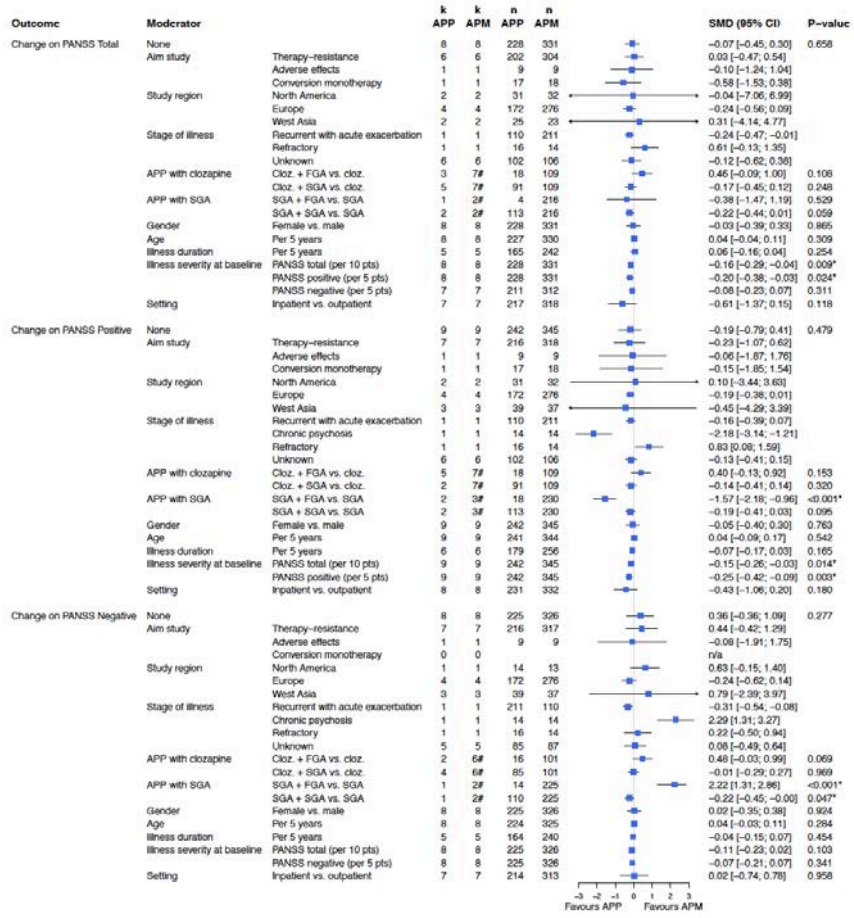


1.a Moderators for response (i.e., ≥ 25% improvement on PANSS total, PANSS positive and negative subscales, or at least minimally improvement on CGI-I (Odds ratios; OR)

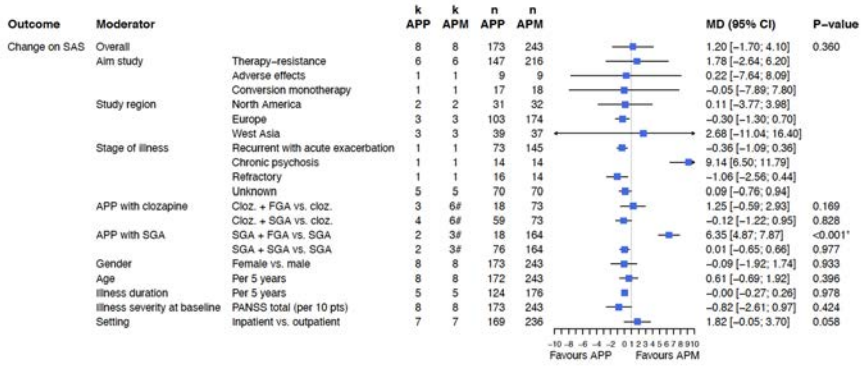


Outcome	Moderator		k APP	k APM	n APP	n APM	MD (95% CI)	P-value
Change on PANSS Total	None		8	8	228	331	−1.08 [−5.69; 3.53]	0.596
	Aim study	Therapy−resistance	6	6	202	304	−0.01 [−6.15; 6.13]	
		Adverse effects	1	1	9	9	−1.11 [−14.03; 11.81]	
		Conversion monotherapy	1	1	17	18	−7.23 [−19.01; 4.55]	
	Study region	North America	2	2	31	32	−0.41 [−88.97; 88.15]	
		Europe	4	4	172	276	−2.99 [−8.27; 2.29]	
		West Asia	2	2	25	23	3.28 [−40.36; 46.91]	
	Stage of illness	Recurrent with acute exacerbation	1	1	110	211	−4.19 [−8.34; −0.05]	
		Refractory	1	1	16	14	5.96 [−0.99; 12.92]	
		Unknown	6	6	102	106	−1.67 [−7.46; 4.13]	
	APP with clozapine	Cloz. + FGA vs. cloz.	3	7#	18	109	5.60 [−1.20; 12.20]	0.105
		Cloz. + SGA vs. cloz.	5	7#	91	109	−2.38 [−5.71; 1.04]	0.168
	APP with SGA	SGA + FGA vs. SGA	1	2#	4	216	−4.60 [−23.51; 23.35]	0.655
		SGA + SGA vs. SGA	2	2#	113	216	−3.74 [−7.62; 0.15]	0.060
	Gender	Female vs. male	8	8	228	331	−0.60 [−6.11; 4.88]	0.832
	Age	Per 5 years	8	8	227	330	0.48 [−0.65; 1.62]	0.406
	Illness duration	Per 5 years	5	5	165	242	−0.90 [−2.49; 0.69]	0.269
	Illness severity at baseline	PANSS total (per 10 pts)	8	8	228	331	−2.10 [−3.99; −0.20]	0.031*
		PANSS positive (per 5 pts)	8	8	228	331	−2.77 [−5.45; −0.09]	0.043*
		PANSS negative (per 5 pts)	7	7	211	312	−0.82 [−3.12; 1.48]	0.483
	Setting	Inpatient vs. outpatient	7	7	217	318	−8.00 [−19.71; 3.75]	0.186
Change on PANSS Positive	None		9	9	242	345	−0.50 [−1.90; 0.80]	0.410
	Aim study	Therapy−resistance	7	7	216	318	−0.45 [−2.28; 1.38]	
		Adverse effects	1	1	9	9	−0.22 [−5.00; 4.55]	
		Conversion monotherapy	1	1	17	18	−0.79 [−5.48; 3.90]	
	Study region	North America	2	2	31	32	0.52 [−18.81; 19.84]	
		Europe	4	4	172	276	−0.87 [−1.89; 0.15]	
		West Asia	3	3	39	37	−0.19 [−6.69; 6.31]	
	Stage of illness	Recurrent with acute exacerbation	1	1	110	211	−0.98 [−2.38; 0.42]	
		Chronic psychosis	1	1	14	14	−2.50 [−3.33; −1.67]	
		Refractory	1	1	16	14	2.52 [0.36; 4.68]	
		Unknown	6	6	102	106	−0.48 [−1.66; 0.70]	
	APP with clozapine	Cloz. + FGA vs. cloz.	5	7#	18	109	1.61 [−0.88; 3.93]	0.183
		Cloz. + SGA vs. cloz.	2	7#	91	109	−0.79 [−1.95; 0.45]	0.195
	APP with SGA	SGA + FGA vs. SGA	2	3#	18	230	−1.13 [−4.45; 2.21]	0.522
		SGA + SGA vs. SGA	2	3#	113	230	−1.06 [−2.34; 0.19]	0.101
	Gender	Female vs. male	9	9	242	345	−0.36 [−2.20; 1.48]	0.706
	Age	Per 5 years	9	9	241	344	0.02 [−0.35; 0.40]	0.906
	Illness duration	Per 5 years	6	6	179	256	−0.39 [−0.91; 0.14]	0.147
	Illness severity at baseline	PANSS total (per 10 pts)	9	9	242	345	−0.66 [−1.28; −0.04]	0.038*
		PANSS positive (per 5 pts)	9	9	242	345	−1.21 [−2.10; −0.32]	0.008*
	Setting	Inpatient vs. outpatient	8	8	231	332	−1.27 [−2.97; 0.67]	0.298
Change on PANSS Negative	None		8	8	225	326	0.70 [−0.90; 2.40]	0.310
	Aim study	Therapy−resistance	7	7	216	317	0.87 [−1.01; 2.76]	
		Adverse effects	1	1	9	9	−0.22 [−4.50; 3.30]	
		Conversion monotherapy	0	0			n/a	
	Study region	North America	1	1	14	13	2.12 [−0.36; 4.61]	
		Europe	4	4	172	276	0.34 [−3.86; 4.53]	
		West Asia	3	3	39	37	1.20 [−1.73; 4.13]	
	Stage of illness	Recurrent with acute exacerbation	1	1	211	110	−1.60 [−2.89; −0.32]	
		Chronic psychosis	1	1	14	14	2.07 [1.42; 2.72]	
		Refractory	1	1	16	14	0.66 [−1.53; 2.86]	
		Unknown	5	5	85	87	0.99 [−1.70; 3.68]	
	APP with clozapine	Cloz. + FGA vs. cloz.	2	6#	16	101	1.75 [−0.26; 3.72]	0.092
		Cloz. + SGA vs. cloz.	4	6#	85	101	−0.24 [−1.24; 0.78]	0.643
	APP with SGA	SGA + FGA vs. SGA	1	2#	14	225	2.51 [−0.90; 5.93]	0.139
		SGA + SGA vs. SGA	1	2#	110	225	−1.25 [−2.42; −0.24]	0.027*
	Gender	Female vs. male	8	8	225	326	0.14 [−1.50; 1.79]	0.868
	Age	Per 5 years	8	8	224	325	0.09 [−0.24; 0.43]	0.594
	Illness duration	Per 5 years	5	5	164	240	−0.18 [−0.68; 0.32]	0.481
	Illness severity at baseline	PANSS total (per 10 pts)	8	8	225	326	−0.42 [−1.01; 0.16]	0.154
		PANSS negative (per 5 pts)	8	8	225	326	−0.29 [−0.95; 0.36]	0.380
	Setting	Inpatient vs. outpatient	7	7	214	313	0.80 [−2.67; 0.72]	0.474
Change on CGI−S	None		9	9	278	192	−0.10 [−0.30; −0.10]	0.280
	Aim study	Therapy−resistance	6	6	161	244	−0.04 [−0.39; 0.30]	
		Adverse effects	1	1	9	9	−0.22 [−0.95; 0.51]	
		Conversion monotherapy	2	2	22	25	−0.30 [−1.98; 1.38]	
	Study region	North America	2	2	31	32	−0.05 [−4.85; 4.74]	
		Europe	4	4	122	209	−0.16 [−0.56; 0.24]	
		West Asia	3	3	39	37	−0.11 [−0.97; 0.75]	
	Stage of illness	Recurrent with acute exacerbation	1	1	90	170	−0.42 [−0.70; −0.15]	
		Chronic psychosis	1	1	14	14	−0.43 [−1.04; 0.18]	
		Refractory	1	1	16	14	0.24 [−0.27; 0.75]	
		Unknown	6	6	72	80	−0.02 [−0.28; 0.23]	
	APP with clozapine	Cloz. + FGA vs. cloz.	3	7#	18	83	0.10 [−0.20; 0.40]	0.508
		Cloz. + SGA vs. cloz.	4	7#	61	83	0.04 [−0.16; 0.23]	0.706
	APP with SGA	SGA + FGA vs. SGA	2	3#	18	189	−0.23 [−0.79; 0.58]	0.448
		SGA + SGA vs. SGA	2	3#	93	189	−0.37 [−0.61; −0.13]	0.003*
	Gender	Female vs. male	9	9	192	278	−0.03 [−0.38; 0.33]	0.879
	Age	Per 5 years	9	9	191	278	−0.03 [−0.10; 0.04]	0.446
	Illness duration	Per 5 years	6	6	162	223	−0.07 [−0.17; 0.03]	0.166
	Illness severity at baseline	PANSS total (per 10 pts)	8	8	187	271	−0.14 [−0.27; −0.01]	0.041*
		Per 1 point CGI−S	9	9	192	278	0.06 [−0.14; 0.26]	0.571
	Setting	Inpatient vs. outpatient	8	8	181	265	0.31 [−0.67; 0.06]	0.108

1.b Moderators for change from baseline on PANSS and CGI-S (mean differences; MD)



1.c Moderators for change from baseline on PANSS (standardized mean differences; SMD)



1.d Moderators for extrapyramidal side effects on SAS (mean differences; MD)

Legend figures 1a – d: APM=a ntipsychotic monotherapy, APP=antipsychotic polypharmacy, CGI-I=Clinical Global Impressions Improvement scale, CGI-S=Clinical Global Impressions Severity scale, CI=confidence interval, Cloz.=clozapine, FGA=first generation antipsychotic, k=number of datasets, MD=mean difference, n=number of patients, OR=odds ratio, PANSS=Positive and Negative Syndrome Scale, SAS=Simpson-Angus extrapyramidal side effects Scale, SGA=second generation antipsychotic, SMD=standardized mean difference

* = p value <0.05

= In the analyses of combinations of antipsychotics, the number of datasets in the APP group is not always equal to the number of datasets in the APM group. This is because we analyzed all clozapine (or SGA) combinations in one analysis. Consequently, in the APM group patients from the placebo conditions from both combinations are included. For example, in the first row of the analysis of APP with clozapine, the APP group contains only studies with patients who had clozapine with FGA, whereas the APM group contains the APM groups from the studies that compared clozapine with FGA to clozapine, and studies that compared clozapine with SGA to clozapine.

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Chapter 7

Summary and general discussion

Summary and main findings

As described in the introductory Chapter 1, polypharmacy, broadly defined as the simultaneous use of multiple medications by one patient, has a long and controversial history. As in general medicine, polypharmacy is common in psychiatry. Polypharmacy with psychiatric medications can be applied to treat comorbid psychiatric disorders and to treat refractory symptoms of a single psychiatric condition, and its increase parallels the development and availability of new psychotropic medications since the 1950s (Sarkar, 2017; Mojtabai and Olfson, 2010). We discussed that patients with difficult-to-treat psychotic symptoms are often prescribed combinations of antipsychotics (antipsychotic polypharmacy; APP). APP can be defined as the simultaneous use of two different antipsychotic medications by one patient (Ijaz et al., 2018). In the literature, definitions vary mainly in the duration of APP, related to the effort to exclude transient APP due to switching of antipsychotics (Foster and King, 2020). Persistent APP for more than 30 days is present in approximately 20% of patients with psychotic disorders worldwide (Gallego et al., 2012; Foster and King, 2020), primarily to treat refractory symptoms. However, the evidence for efficacy is weak, and guidelines for the treatment of psychotic disorders therefore advocate antipsychotic monotherapy (APM) and advice to restrict APP to cross-titration during switching of antipsychotics and as an option in patients with treatment-resistant schizophrenia (Moore et al., 2007; Kuipers et al., 2014; van Alphen et al., 2012; American Psychiatric Association, 2020). We have pointed out that, based on the basic medical axiom "*primum non nocere*" (first, do no harm), it is important to carefully consider both the potential benefits and harms of antipsychotic polypharmacy.

As elaborated in the general introduction in Chapter 1, rational polypharmacy according to Preskorn & Lacey includes twelve criteria, of which the most important are: evidence that the combination of medications will have a beneficial effect on the pathoetiology (the cause) or pathophysiology (the associated abnormal physiological changes) of the disorder; must be more (cost)effective than monotherapy; must not pose significantly greater safety or tolerability risks than monotherapy due to pharmacokinetic and/or pharmacodynamic properties; and the medications involved must have different mechanisms of action (Preskorn and Lacey, 2007). The latter criterion is particularly relevant when considering APP in schizophrenia and other psychotic disorders. The dopamine hypothesis and subsequent elaborations have been the dominant explanatory model since the late 1960s (Van Rossum, 1967), although there is increasing recognition of the heterogeneity of the disorder (Keshavan et al., 2011). This hypothesis proposes

that dysregulation and imbalance of dopaminergic function in the brain is a key mechanism in the pathophysiology of schizophrenia, with striatal presynaptic hyperdopaminergia involving D_2 receptors underlying psychotic symptoms and cortical hypodopaminergia involving D_1 receptors underlying cognitive symptoms (McCutcheon et al., 2020; Kaar et al., 2020). Except for a very recently approved antipsychotic targeting muscarinic receptors (Kaul et al., 2024b), all antipsychotics approved to date share their ability to block striatal postsynaptic D_2 receptors either as a dopamine antagonist or as a partial dopamine agonist, thus acting through this same putative mechanism of action (Lieberman and First, 2018; Miyamoto et al., 2012). Combining these medications is a form of same-class polypharmacy, although many of them also have properties that affect several other neuroreceptors, which may contribute to their efficacy in other ways. Given the often conflicting and inconclusive results of studies on the efficacy of APP, we aimed to investigate as to which patients with psychotic disorders may benefit from APP and whether these potential benefits outweigh possible harms. The results may contribute to a more appropriate use of APP in patients with psychotic disorders.

First, in an exploratory study described in **Chapter 2**, we examined the extent to which psychiatrists agree in judging the rationality of medication prescriptions in clinical vignettes with varying degrees of polypharmacy of psychiatric medications (psychiatric polypharmacy). We found that the agreement among all raters across all vignettes was poor, barely exceeding agreement by chance (inter-rater correlation coefficient 0.109, 95% CI=0.006–0.295; $p<0.005$), with a trend toward greater disparities as the number of medications prescribed increases. Although the study was small and replication would be useful, these alarming findings suggest that the quality of prescriptions involving polypharmacy with psychiatric medications may be compromised as the complexity of a drug regimen increases, suggesting "eminence-based" rather than evidence-based prescribing.

Focusing on the common practice of APP in psychotic disorders, we conducted a systematic review of randomized controlled trials (RCTs) and meta-analyses described in **Chapter 3.** We summarized the evidence for the rationality of APP using the above criteria of Preskorn & Lacey (Preskorn and Lacey, 2007), operationalized in terms of underlying support for neurobiological mechanisms of action, efficacy, tolerability, and cost-effectiveness. In this review, we found no preclinical studies to support the various neurobiological hypotheses underlying APP and no additional evidence of efficacy, which remains inconclusive with only modest overall beneficial clinical relevance. APP was associated with several potentially serious adverse effects and increased health care costs. These findings

support adherence to existing clinical guidelines for the treatment of psychotic disorders, which advocate antipsychotic monotherapy and limit APP to patients with clozapine-refractory psychosis.

This prompted us to conduct a quality improvement study at our hospital to reduce inappropriate APP, which we reported on in **Chapter 4.** In this serial intervention study, we compared the effect of a general intervention with the effect of an additional personalized guideline-based e-mail intervention on the prevalence of episodes of persistent APP lasting more than 30 days. The general intervention did not appear to be effective, but the addition of a personalized intervention significantly reduced episodes of persistent APP by nearly 50% and patient days with APP by 35%. This finding may reflect improved adherence to treatment guidelines for patients with schizophrenia and other psychotic disorders. However, we were not able to verify whether this reduction in APP resulted in better clinical outcomes because we did not have clinical data from the patients involved. It is important to note that although 50% of the episodes on APP were discontinued, the other 50% of the APP episodes were continued. Continuation of APP may reflect physician reluctance to reduce APP, but it may also indicate that some patients have benefited from APP (Tiihonen et al., 2019; Lahteenvuo and Tiihonen, 2021; Bighelli et al., 2022).

This study also provided the opportunity to prospectively explore physicians' reasons for initiating and continuing APP in patients with schizophrenia spectrum disorders, which we described in **Chapter 5**. Clinicians' reasons for prescribing APP have been investigated in cross-sectional studies, but very few have used a prospective design. We found that APP was initiated primarily for cross-titration switching of antipsychotics and, to a lesser extent, to reduce agitation and/or sleep problems or to treat refractory psychotic symptoms. This is in contrast to the results of previous cross-sectional studies, in which persistent APP was typically associated with the treatment of refractory psychotic symptoms (Sernyak and Rosenheck, 2004; Gallego et al., 2012). At follow-up, APP was discontinued in approximately 50% of these patients. Although most indications for APP at initiation were consistent at follow-up, we found that in 29% of patients initiated on APP for cross-titration switching of antipsychotics, the switch was not completed and the patient and prescriber were "trapped" in cross-titration, resulting in unintended and potentially unnecessary persistent APP.

Given the mixed results of clinical trials and the inconclusive results of meta-analyses on the efficacy of APP as summarized in Chapter 3, the results of discontinuation

studies (Bighelli et al., 2022), and new emerging evidence on the effectiveness of APP from nationwide real-world studies (Tiihonen et al., 2019; Lahteenvuo and Tiihonen, 2021), we hypothesized that there are patients who may benefit from APP. Therefore, we initiated the final study of this thesis, the first individual patient data meta-analysis (IPDMA) which aimed to identify characteristics of patients with schizophrenia spectrum disorders who benefit from APP. The results of this study are reported in **Chapter 6**. We found that the efficacy of APP compared with antipsychotic monotherapy (APM) depends on the severity of the psychotic episode. APP is more effective in patients with high baseline PANSS total scores and predominantly positive symptoms. Extrapyramidal side effects increased significantly when a first-generation antipsychotic was combined with a second-generation antipsychotic, emphasizing that the potential beneficial effect on clinical symptoms must be carefully weighed against the potential for increased side effects.

General discussion

Mental disorders are categorized according to their predominant symptoms, such as anxiety, mood, personality, and psychotic disorders (American Psychiatric Association, 2013). The etiology and pathophysiology of these disorders is unclear, and there is often co-occurrence of symptoms and thus overlap of disorders. This may encourage physicians to prescribe various types of polypharmacy in psychiatry, such as same-class, multi-class, adjunctive, and augmentation polypharmacy. Therefore, as in general medicine, the use of polypharmacy in psychiatry may be difficult to avoid and is sometimes even necessary to stabilize or improve a patient's severe condition. However, as found in this thesis, there is evidence that as the number of psychotropic medications prescribed increases, psychiatrists' agreement about the rationality of the medication prescribing tends to decrease. This can compromise the quality of medication prescribing, with potentially inappropriate combinations and increased risk of medication interactions.

The treatment of patients with persistent psychotic symptoms that not have responded to antipsychotic monotherapy (including clozapine, the only approved antipsychotic for treatment-resistant psychotic symptoms)(Meltzer, 1997) is challenging, and psychiatrists often resort to APP. In general, Dutch and international guidelines for the treatment of patients with psychotic disorders recommend caution with this treatment, due to inconsistent evidence of efficacy and concerns about safety (van Alphen et al., 2012; American Psychiatric Association, 2020) At the same time, these guidelines provide only limited evidence-based recommendations

for treatment decisions in patients with treatment-resistant psychotic symptoms, and include APP as an option that may be beneficial for unspecified subgroups of patients (van Alphen et al., 2012; American Psychiatric Association, 2020). This ambiguity can confuse physicians, may allow for inappropriate and persistent APP, and needs to be addressed.

Our review of randomized trials and meta-analyses found little or no evidence for any underlying neurobiological mechanisms of action supporting APP, nor for short-term outcomes of efficacy, safety, and cost-effectiveness. Although this 2013 publication may be considered out of date, we have not found any new randomized controlled trials or meta-analyses since then, suggesting that these conclusions remain valid. However, clinical trials typically have a limited number of patients (a few hundred at most), follow-up is often no longer than 6 months, and have high internal validity but often at the expense of external validity (generalizability). This makes them well suited for investigating short-term effects in a specific population, but less suited for assessing long-term treatment effects. Observational studies, which can enroll tens of thousands of patients from large electronic databases, may provide more generalizable long-term clinical outcomes of APP prescribing. Although such studies bear the risk of increased selection bias for exposure to APP or APM, selection bias due to patient characteristics can be overcome in a within-individual design (Tiihonen et al., 2019). In addition to RCTs, such studies are highly relevant to investigate the effectiveness (i.e., combined efficacy and tolerability data) and safety of APP compared with monotherapy in patients with lifelong disorders such as schizophrenia and related psychotic disorders. In these patients, their well-being is determined not only by short-term symptom reduction, but also by long-term outcomes in social functioning, relapse hospitalizations, somatic comorbidity, and mortality (Taipale et al., 2020). Recent observational studies, sometimes using a within-individual design, have provided evidence of better outcomes of APP compared with monotherapy on long-term outcomes such as psychiatric hospitalizations for relapse, admission to a general hospital, and mortality (Tiihonen et al., 2019; Katona et al., 2014). They also provided evidence on the safety of APP in terms of hospitalization for physical health problems (Taipale et al., 2023). These findings challenge current guidelines which recommend to refrain from APP (van Alphen et al., 2012; American Psychiatric Association, 2020; Moore et al., 2007).

Although it is notoriously difficult to get clinicians to adhere to existing guidelines (Bauer, 2002; Bero et al., 1998), we found that repeated, personalized, guideline-based feedback reduced APP by about half. However, the other half of the APP prescriptions persisted at 60 days. For most patients with persistent APP, the

indication at initiation remained consistent over time, most often to treat refractory symptoms. But a key finding was that in about a quarter of patients with APP who were initiated to switch antipsychotics, the switch was not completed and APP persisted, with the physician sometimes reporting that the patient improved during the switch. This is sometimes referred to as the cross-titration trap, where the clinician and patient are "caught" in cross-titration because the patient improves while on both antipsychotics and the combination is continued (Stahl, 1999). It has been recognized in cross-sectional studies (Tapp et al., 2003), but has not been demonstrated in a prospective design up to now. To avoid this cross-titration trap and potentially unnecessary persistent APP, it is important to complete the intended switch. It is also important to keep this switch as short in time as possible, as there is evidence that patients on APP that is prescribed for 30 days are likely to continue on the combination (Tapp et al., 2003), which was confirmed in our data.

There is a paucity of research on the best way to switch antipsychotics. A systematic review has summarized that immediate discontinuation of the primary antipsychotic was associated with dopamine hypersensitivity syndromes (e.g., hypersensitivity psychosis and withdrawal dyskinesia), rebound syndromes (related to cholinergic, histaminergic, and serotonergic activity), and worsening of psychotic symptoms, whereas gradual cross-over switching was associated with an increased risk of side effects (Takeuchi et al., 2017). However, in a meta-analysis of these studies, there was evidence that immediate discontinuation of the current antipsychotic did not differ from gradual cross-titration switching with respect to study discontinuation, psychopathology, extrapyramidal symptoms, and other treatment-emergent adverse effects (Takeuchi et al., 2017). Therefore, we recommend to keep the duration of the combined antipsychotic prescription as short as possible, preferably within 30 days, and completing the switch ending with monotherapy on the new antipsychotic. The switch should also be tailored to the patient's clinical condition, as symptoms of dyskinesia may indicate dopamine hypersensitivity with a potentially greater risk of withdrawal or rebound psychosis (Yin et al., 2017). It should also be adapted to the antipsychotics involved in the switch, especially if the primary antipsychotic has a high muscarinic receptor affinity, which increases the risk of cholinergic withdrawal or rebound syndromes (Cerovecki et al., 2013).

Our finding that approximately 50% of APP episodes were continued despite a personalized, guideline-based intervention raises the question of whether these clinicians were too reluctant to adhere to guidelines or whether they had good reasons for not converting to monotherapy. Our data did not allow us to answer

this question, but this finding may be consistent with the results of randomized controlled trials of APP discontinuation, which have shown that some patients may deteriorate after converting to a single antipsychotic (Constantine et al., 2015; Borlido et al., 2016; Essock et al., 2011). Although discontinuation of APP was immediate in these studies, deterioration often occurred after several months (Constantine et al., 2015; Essock et al., 2011). This makes it unlikely that the deterioration is due to withdrawal symptoms (which typically occur in the first week after discontinuation and usually disappear within four weeks) (Brandt et al., 2020; Cerovecki et al., 2013). However, it cannot be ruled out that deterioration may also have been caused by rebound psychosis due to dopamine hypersensitivity (supersensitivity psychosis), which often occurs about 6 weeks after discontinuation, but can also occur within 1 to 2 years after stopping APP (Cerovecki et al., 2013; Yin et al., 2017).

When examining the characteristics of patients who benefit from APP in our IPDMA, another key finding was that severely ill psychotic patients with predominantly positive symptoms may have the best chance of benefiting from APP in terms of reducing psychopathology, although we could not determine from our data which combinations were more or less beneficial. This effect was not modified by stage of illness, suggesting that both severely ill patients with acute exacerbations and those with chronic refractory psychosis may benefit from APP. Unlike the nationwide cohort studies, in this IPDMA we did not have data on physical morbidity or mortality outcomes. Also, because this was a predominantly inpatient population, we could not determine the effects of APP compared with monotherapy on admissions.

Unfortunately, despite repeated requests, we were only able to include 32% of eligible RCTs with 31% of all eligible patients in our IPDMA. However, the overall comparison of studies from which we could and could not obtain IPD showed that the included studies were a representative sample of all studies conducted in this field, and we were able to include almost 100% of the patients from these RCTs. Nevertheless, the overall retrieval rate of IPD was rather low, considering that a meta-analysis showed that approximately 90% of the included IPDMAs were able to enroll more than 50% of the eligible IPD (Wang et al., 2021). This low inclusion rate was due to non-response to IPD requests (48%), willingness to cooperate without follow-up (19%), untraceable records (19%), and refusal to cooperate (14%). In particular, the unavailability of IPD from two large RCTs with a total of 530 patients (27% of all eligible IPD) was very disappointing; one study was unavailable because the principal investigator refused to participate outright, and the other because

the involved investigators were denied access to the data by the pharmaceutical company that had sponsored the trial. To make progress in determining the role of APP in the treatment of patients with difficult-to-treat psychotic disorders, we need much larger numbers of patients to have greater statistical power. In addition to the need for more large observational studies, this will require better collaboration between investigators in clinical trials, for example in future IPDMAs. We strongly encourage researchers and pharmaceutical companies to be willing to share their data for such studies.

An important question to be answered is how to understand the beneficial effect of APP in more severely ill patients that we have found. There is no theoretical basis for a combination of antipsychotics to have a beneficial effect on the pathoetology and/or pathophysiology compared with antipsychotic monotherapy. All approved antipsychotics act by 60-80% blockade of the striatal postsynaptic D_2 receptor. As a form of same-class polypharmacy, the antipsychotics involved in APP do not have different mechanisms of action, and if a single antipsychotic is appropriately dosed, no additional benefit from APP would be expected. In conclusion, there is no theoretical mechanistic basis for expecting APP to be more effective than APM.

However, Kaar and colleagues proposed three potential explanatory mechanisms that may be involved in the superiority of APP over monotherapy (Kaar et al., 2020) which we will discuss in the context of our findings:

1. *APP may lead to greater dopamine D_2 occupancy and blockade which increases efficacy*.

   In our IPDMA, the dose in olanzapine equivalents in the APP condition was almost double that in the monotherapy condition (26.8 versus 15.3 mg olanzapine equivalents). This may result in higher striatal D_2 receptor occupancy in patients treated with APP compared with monotherapy. The validity of this hypothesis can be investigated using molecular imaging techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT). We are aware of only one SPECT study (N=10) comparing D_2 receptor occupancy of clozapine monotherapy (mean dose 500 mg daily) and APP consisting of clozapine (mean dose 450 mg daily) combined with fixed dose haloperidol 4 mg (Mossaheb et al., 2006). They found baseline and endpoint D_2 receptor occupancy of 23.8% and 22.8% in the monotherapy group, respectively, and a significant increase from 21.2% to 65.3% in the APP group. Interestingly, there were no differences in Positive and Negative Syndrome Scale (PANSS) scores between the two

groups. However, there is evidence that patients with multiple psychotic episodes require higher doses of antipsychotics than patients with a first psychotic episode, and the efficacy of antipsychotics for relapse prevention decreased significantly after the second relapse (Taipale et al., 2022). It can be hypothesized that severely ill psychotic patients, as opposed to less severely ill patients, have more upregulation of dopamine receptors and more frequent dopamine hypersensitivity than less severely ill patients. This dopamine hypersensitivity may be the iatrogenic result of the cumulative antipsychotic load prescribed to a patient and has been associated with treatment resistance (Yin et al., 2017). As a result, severely ill patients may require a higher antipsychotic dose, which was the case on average in our APP group. Although there is evidence of a ceiling effect at a cutoff of 80% D_2 receptor occupancy in a mixed population of first-episode and chronic (but not necessarily treatment-resistant) patients (Yilmaz et al., 2012), it may be that treatment-resistant patients represent a distinct group that requires D_2 receptor occupancy greater than 80% for optimal efficacy. Less severely ill patients may have less dopamine hypersensitivity, allowing them to achieve sufficient efficacy with a normal dose of antipsychotic monotherapy. This may explain why the additional beneficial effect of APP was not observed in less severely ill patients.

From this perspective, it would be interesting to know whether it is possible to treat this subgroup of severely ill patients with a supratherapeutic dose of antipsychotic monotherapy instead of (a cumulative supratherapeutic dose of) APP. If dopamine hypersensitivity is the iatrogenic result of cumulative antipsychotic exposure, it is important to limit antipsychotic treatment to the lowest effective dose and the shortest duration early in the course of the disorder, and to consider additional nonpharmacologic interventions for relapse prevention. This issue is particularly controversial with regard to the duration of antipsychotic treatment in patients with first-episode psychosis (Wunderink et al., 2013; Taipale et al., 2022; Begemann et al., 2020).

2. *Reduction in side effects may increase tolerability*.
APP can be used to reduce the side effects of the primary antipsychotic, such as extrapyramidal symptoms (EPS), weight gain, metabolic disturbances, and prolactin elevation (Hjorth, 2021). This may improve tolerability and lead to better medication adherence. However, we did not find fewer extrapyramidal side effects (EPS) in patients treated with APP compared with those on monotherapy. On the contrary, EPS was significantly more common with the

combination of a first-generation antipsychotic and a second-generation antipsychotic. Scores on the Abnormal Involuntary Movement Scale (AIMS) and the Barnes Akathisia Rating Scale (BARS) were similar and in the lower range in both groups. However, we cannot completely rule out this explanation. We did not have sufficient data for other than motor side effects, and we could not analyze at the drug level whether favorable combinations might have caused fewer side effects.

3. *The addition of a second agent induces beneficial effects via actions at other receptors*. Combination antipsychotics may modulate receptors other than the postsynaptic D2 receptor, which in some unknown way may account for the beneficial effects of APP. This explanation for the superior efficacy of APP in severely ill patients is possible but cannot be confirmed or rejected without a more elaborate theoretical model.

   An additional, more pragmatic explanation for the superiority of APP over monotherapy is that in the real world, adherence to antipsychotics is poor, and if a patient is prescribed two antipsychotics, he or she may use at least one of them (Tiihonen et al., 2019). On the other hand, the complexity of the medication regimen may also increase nonadherence to all prescribed antipsychotics (Kane et al., 2013), making it a less likely explanation for the better outcome of APP in more severely ill patients.

APP versus other options for treatment-resistant psychosis

The use of APP in patients with treatment-resistant psychotic symptoms should be weighed against other options that may be beneficial in addition to antipsychotic monotherapy. Cognitive behavior therapy (CBT) was found to be a moderate effective adjuvant to antipsychotic medication in the treatment of persistent symptoms of schizophrenia and was associated with robust improvements in the positive symptoms that were sustained at follow-up (Rathod et al., 2008; Burns et al., 2014). A systematic overview of meta-analyses investigating 42 pharmacologic cotreatment strategies in addition to antipsychotic monotherapy, including (besides antipsychotics) antidepressants, mood stabilizers, antioxidants, hormones, and miscellaneous medications was inconclusive due to high risk of bias (Correll et al., 2017). Electroconvulsive therapy (ECT) had a positive effect on medium-term clinical response for people with treatment-resistant schizophrenia, but no clear and convincing advantage or disadvantage was found for adding ECT to standard care for other outcomes (Sinclair et al., 2019). In meta-analyses, repetitive transcranial magnetic stimulation (rTMS) had only small to modest beneficial effects

over placebo for positive, negative, and cognitive symptoms (Mehta et al., 2019). A systematic review suggested that deep transcranial magnetic stimulation (dTMS) does not reduce psychotic symptoms in schizophrenia, but it shows potential for improving executive functions (Mo et al., 2024).

Future Directions

As discussed above, until very recently, all antipsychotics approved for the treatment of patients with schizophrenia or psychotic disorders act primarily by blocking postsynaptic dopamine receptors, which is largely downstream of the hypothesized key striatal dopamine abnormalities in schizophrenia and other psychotic disorders. In addition, these antipsychotics do not normalize presynaptic dopamine abnormalities. And although blocking of postsynaptic D_2 receptors reduces aberrant dopamine signaling, it also interferes with physiological signaling that is essential for adaptive learning, motivated behavior, motor, and other functions. It may increase side effects, decrease social functioning, and lead to non-adherence. APP with currently approved D_2 blocking antipsychotics is therefore unlikely to be a promising future approach for treating patients with treatment-resistant psychotic symptoms, despite the beneficial effects that we have found in the IPDMA in severely ill patients.

In the future, it may be important to develop medications that downregulate striatal presynaptic hyperdopaminergia, allowing normal physiological dopaminergic function in the striatum and cortex. Medications that are effective in treating psychotic symptoms in this way may represent a new class of antipsychotics. Interesting advances in this field include the development of compounds targeting the vesicular monoamine transporter (VMAT), dopamine D_2 autoreceptors, trace amine type 1 receptors (TAAR1), the gamma-aminobutyric acid (GABA) receptor, the glutamatergic receptor, and the muscarinic M4 receptor (see Figure 1)(Kaar et al., 2020). In total, approximately 16 non-dopaminergic compounds are being investigated as monotherapy or add-on therapy in Phase II or Phase III trials (Komatsu et al., 2024). Recently, in September 2024, the first compound targeting muscarinic receptors (xanomeline-trospium combination) showed efficacy in reducing positive and negative symptoms in patients with schizophrenia (Kaul et al., 2024a; Kaul et al., 2024b), and was approved by the FDA as the first non-dopaminergic antipsychotic for the treatment of schizophrenia in adults (https://www.fda.gov/news-events/press-announcements/fda-approves-drug-new-mechanism-action-treatment-schizophrenia, accessed October 4, 2024). Such new antipsychotics with a mechanism of action that is different from classical postsynaptic D_2-blocking, if not effective as monotherapy, may potentially be

combined with the traditional class of dopamine-blocking antipsychotics in a more rational form of APP in difficult-to-treat psychotic patients.

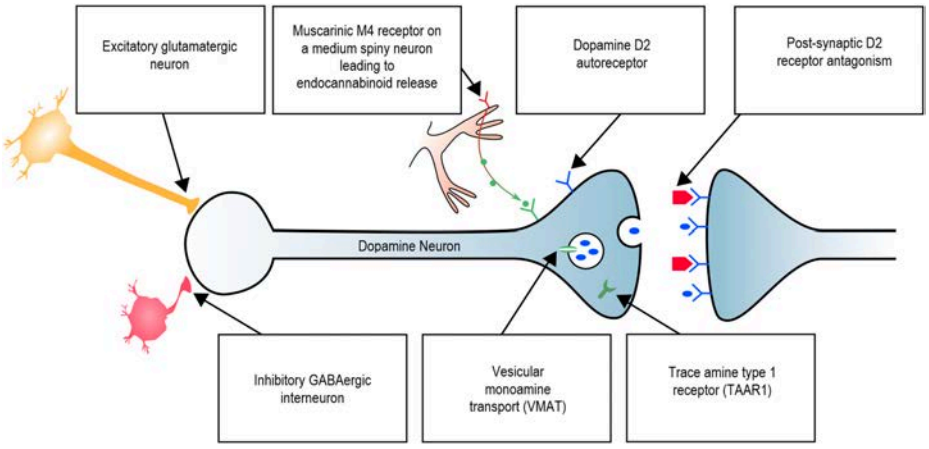

Fig. 1. Potential new treatment targets in schizophrenia. The figure shows current antipsychotics primarily act at D2 receptors downstream of the main dopamine abnormalities in schizophrenia and summarizes alternative, potential mechanisms to regulate dopamine neuron function. Blocking the vesicular monoamine transporter, activating dopamine D2 autoreceptors or trace amine type 1 receptors, or modulating the retrograde activation of cannabinoid type 1 receptors by endocannabinoids are approaches that could directly target presynaptic dopamine dysregulation. Alternatively, targeting the upstream regulation of dopamine neuron activity via gamma aminobutyric (GABA)ergic or glutamatergic projections could be used to normalize dopamine neuron function.

Legend: =dopamine =dopamine D2 antagonist = dopamine receptor.

Source: (Kaar et al., 2020)

In contrast to the theory of presynaptic hyperdopaminergica in patients with schizophrenia, an intriguing finding is that this hyperdopaminergica may not be present in patients with treatment-resistant schizophrenia (Spark et al., 2022). This suggests that non-treatment-resistant and treatment-resistant patients may be distinct groups based on their dopamine synthesis capacity, with the latter not responding well to conventional D_2-blocking antipsychotics including clozapine, or antipsychotic combinations (Spark et al., 2022). This finding also challenges the dopamine theory as a sufficient explanatory model for treatment-resistant psychotic symptoms, and suggests the need for more comprehensive models that may include hypofrontostriatal connectivity and the role of glutamate(Spark et al., 2022).

General conclusions

Antipsychotic polypharmacy (APP) in clinical practice to date has consisted of combining two antipsychotic agents that primarily target the striatal postsynaptic D2 receptor in a form of same-class polypharmacy. The evidence for the efficacy and safety of APP from the systematic reviews and meta-analyses that we reviewed is weak and inconclusive. We have shown that personalized, guideline-based instructions can reduce APP to some extent. We have found that cross-titration switching of antipsychotics poses a risk for the emergence of potentially inappropriate persistent APP if a patient improves during the switch and the switch is therefore not completed. This is sometimes referred to as the cross-titration trap. We have also found that there is a subgroup of difficult-to-treat psychotic patients who may benefit from APP. This subgroup consists of more severely psychotic patients with predominantly positive symptoms. However, it remains unclear which combinations of agents are most effective and what the mechanism of action is, which warrants further research. Given the efficacy of clozapine on symptom reduction in patients with treatment-resistant psychotic disorders, it is important that treatment with clozapine be tried first before applying APP. These conclusions may give APP a clearer position in future guidelines for the treatment of psychotic disorders, especially considering the results in areas other than mere symptom reduction.

Recommendations

There are two main recommendations from this scientific study:

1. APP may be beneficial in reducing psychopathology in severely ill psychotic patients with predominantly positive symptoms that have insufficiently responded to treatment with clozapine. This information resulting from an IPDMA is the best currently available, and it is important that it is made available to practitioners of patients with treatment-resistant psychotic disorders by being included in future updates of guidelines for the treatment of patients with psychotic disorders.
2. Gradual cross-titration switching is a major risk factor for potentially inappropriate, persistent APP, sometimes referred to as the "cross-titration trap". Optimal antipsychotic switching has not been well studied but must be tailored to the needs of the patient and the antipsychotics involved. Consideration should be given to whether immediate tapering of the current antipsychotic is feasible to avoid this type of APP.

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Appendix

Nederlandse samenvatting
(Summary in Dutch)

Dankwoord (Acknowledgements)

Curriculum Vitae

List of Publications

PhD Portfolio

Data Management Statement

Donders Graduate School for Cognitive Neuroscience

Nederlandse samenvatting (Summary in Dutch)

Samenvatting en belangrijkste bevindingen

In het inleidende hoofdstuk 1 beschreven we dat polyfarmacie, gedefinieerd als het gelijktijdig gebruik van meerdere medicijnen door één patiënt, een lange en controversiële geschiedenis heeft. Net als in de algemene geneeskunde komt polyfarmacie ook veel voor in de psychiatrie. Polyfarmacie met psychiatrische medicatie (psychiatrische polyfarmacie) kan worden toegepast om comorbide psychiatrische stoornissen te behandelen en om refractaire symptomen van één psychiatrische aandoening te behandelen. De toename in toepassing van psychiatrische polyfarmacie loopt parallel met de ontwikkeling en beschikbaarheid van nieuwe psychofarmaca sinds de jaren '50 van de vorige eeuw (Sarkar, 2017; Mojtabai and Olfson, 2010). We bespraken dat patiënten met moeilijk te behandelen psychotische symptomen vaak combinaties van antipsychotica voorgeschreven krijgen (antipsychotische polypharmacy; APP). APP kan gedefinieerd worden als het gelijktijdige gebruik van twee verschillende antipsychotische medicijnen door één patiënt (Ijaz et al., 2018). In de literatuur worden diverse definities voor APP gebruikt, die vooral verschillen in de duur van de toepassing van APP. Dit heeft vooral te maken heeft met het streven om tijdelijke APP gedurende het wisselen van antipsychotica uit te sluiten (Foster and King, 2020). Langdurige APP gedurende meer dan 30 dagen komt wereldwijd voor bij ongeveer 20% van de patiënten met psychotische stoornissen (Foster and King, 2020; Gallego et al., 2012), voornamelijk om therapieresistente symptomen te behandelen. Maar het bewijs voor de werkzaamheid van APP is echter zwak. Richtlijnen voor de behandeling van patiënten met psychotische stoornissen pleiten daarom voor antipsychotische monotherapie (APM) en adviseren om APP tijdelijk te gebruiken bij het kruislings omzetten van antipsychotica en als een optie bij de behandeling van patiënten met therapieresistente schizofrenie die onvoldoende baat hebben gehad bij en behandeling met clozapine of bij wie dit niet mogelijk is (Moore et al., 2007; Kuipers et al., 2014; van Alphen et al., 2012; American Psychiatric Association, 2020). We hebben erop gewezen dat het vanuit het medisch adagium "*primum non nocere*" (ten eerste geen kwaad doen) belangrijk is om zowel de potentiële voordelen als de nadelen van antipsychotische polyfarmacie zorgvuldig te overwegen.

Zoals uitgewerkt in de inleiding in hoofdstuk 1, omvat rationele polyfarmacie volgens Preskorn & Lacey twaalf criteria, waarvan de belangrijkste zijn: bewijs dat de combinatie van medicijnen een gunstig effect zal hebben op de pathoetiologie (de oorzaak) of pathofysiologie (de hiermee gepaard gaande abnormale fysiologische veranderingen) van de stoornis; de combinatie moet (kosten)effectiever zijn

dan monotherapie; de combinatie mag geen significant grotere veiligheids- of verdraagbaarheidsrisico's met zich meebrengen vergeleken met monotherapie vanwege hun farmacokinetische en/of farmacodynamische eigenschappen; en de betrokken medicijnen moeten verschillende werkingsmechanismen hebben (Preskorn and Lacey, 2007). Dit laatste criterium is relevant wanneer we APP beschouwen bij schizofrenie en andere psychotische stoornissen. De dopaminehypothese en de latere uitwerkingen hiervan zijn het belangrijkste verklaringsmodel voor schizofrenie en verwante psychotische stoornissen sinds het einde van de jaren '60 van de vorige eeuw (Van Rossum, 1967), hoewel er ook steeds meer erkenning komt voor de heterogeniteit van deze aandoeningen (Keshavan et al., 2011). Sterk vereenvoudigd veronderstelt deze hypothese dat ontregeling en onbalans van de dopaminerge activiteit in de hersenen een centraal mechanisme is in de pathofysiologie van schizofrenie. Presynaptische dopaminerge hyperactiviteit in het striatum met overmatige stimulering van postsynaptische dopamine D_2-receptoren zou aan de basis liggen van psychotische symptomen, en corticale presynaptische dopaminerge hypoactiviteit met onvoldoende activatie van postsynaptische dopamine D_1-receptoren zou aan de basis liggen van cognitieve symptomen (McCutcheon et al., 2020; Kaar et al., 2020). Met uitzondering van een zeer recent in de Verenigde Staten goedgekeurd antipsychoticum dat zich richt op de presynaptische muscarine receptor (Kaul et al., 2024), hebben alle tot op heden geregistreerde antipsychotica de eigenschap om postsynaptische D_2-receptoren in het striatum te blokkeren, hetzij als een dopamineantagonist of als een partiële dopamineagonist, waarmee ze allemaal een vergelijkbaar werkingsmechanisme hebben (Lieberman and First, 2018; Miyamoto et al., 2012). Het combineren van deze antipsychotische medicijnen is dus een vorm van polyfarmacie van dezelfde neurofarmacologische klasse, hoewel veel van deze medicijnen ook eigenschappen hebben die verschillende andere neuroreceptoren beïnvloeden, wat mogelijk ook zou kunnen bijdragen aan hun werkzaamheid. Gezien de vaak tegenstrijdige en onduidelijke resultaten van onderzoeken naar de werkzaamheid van APP, wilden wij onderzoeken welke patiënten met psychotische stoornissen baat kunnen hebben bij APP en of de potentiële voordelen opwegen tegen mogelijke nadelen. De resultaten hiervan kunnen bijdragen aan een meer adequate toepassing van APP bij de behandeling van patiënten met psychotische stoornissen.

Als eerste onderzochten we in een verkennende studie, beschreven in **Hoofdstuk 2**, in hoeverre psychiaters het onderling eens zijn over de rationaliteit van medicatievoorschriften bij vijf klinische vignetten met een variërende mate van psychiatrische polyfarmacie. We vonden dat de overeenstemming tussen alle beoordelaars over alle vignetten zeer gering was, nauwelijks meer dan toeval

(intraclass correlatiecoëfficiënt 0.109, 95% CI=0,006-0,295; p<0,005), met een trend naar grotere verschillen naarmate het aantal voorgeschreven medicijnen toeneemt. Hoewel het onderzoek klein was en herhaling zinvol zou zijn, suggereren deze bevindingen dat de kwaliteit van medicatievoorschriften met psychiatrische polyfarmacie in het geding kan komen als de complexiteit van het medicatieregime toeneemt.

Vervolgens hebben we ons gericht op de rationaliteit van de veel voorkomende toepassing van APP bij psychotische stoornissen en deden een literatuuronderzoek naar de rationaliteit hiervan in de vorm van een systematische review van gerandomiseerde gecontroleerde trials (RCTs) en meta-analyses, die we beschreven in **Hoofdstuk 3.** We hebben de evidentie voor de rationaliteit van APP beoordeeld aan de hand van de eerdergenoemde criteria van Preskorn & Lacey (Preskorn and Lacey, 2007), waarbij we rationaliteit hebben geoperationaliseerd als de evidentie voor een onderliggend neurobiologisch werkingsmechanisme, voor de werkzaamheid, de verdraagbaarheid en voor de kosteneffectiviteit van APP. In deze review vonden we geen preklinische studies die de verschillende neurobiologische hypothesen die aan APP ten grondslag zouden kunnen liggen ondersteunen. We vonden ook geen nieuw bewijs voor de werkzaamheid, deze blijft controversieel en met hooguit bescheiden effectiviteit en klinische relevantie. APP was geassocieerd met verschillende potentieel ernstige bijwerkingen en hogere gezondheidszorgkosten. Deze bevindingen ondersteunen naleving van bestaande richtlijnen voor de behandeling van psychotische stoornissen. Deze richtlijnen bevelen antipsychotische monotherapie aan en adviseren APP tijdelijk te gebruiken bij het switchen van antipsychotica of te overwegen als een behandeloptie bij patiënten met een psychotische stoornis die onvoldoende heeft gereageerd op eerdere behandelingen met antipsychotische monotherapie, inclusief een adequate behandeling met clozapine.

Dit heeft ons er toe gebracht om in ons psychiatrisch ziekenhuis een kwaliteits-verbeteringsstudie uit te voeren om potentieel onnodige APP te verminderen, waarover we rapporteerden in **Hoofdstuk 4.** In deze seriële interventiestudie vergeleken we het effect van een algemene, op de Nederlandse richtlijn voor de behandeling van patiënten met schizofrenie en andere psychotische stoornissen gebaseerde e-mailinterventie met het effect van een aanvullende, gepersona-liseerde e-mailinterventie op de prevalentie van episoden van voortgezette APP die langer dan 30 dagen duurden. De algemene interventie bleek niet effectief, maar de toevoeging van de gepersonaliseerde interventie verminderde het aantal episoden van voortgezette APP met bijna 50% en het aantal patiëntdagen

met APP met 35%. Deze bevindingen kunnen wijzen op een betere naleving van de betreffende behandelrichtlijn. Maar omdat we niet beschikten over klinische gegevens van de betrokken patiënten konden we niet vaststellen of deze afname in de toepassing van APP ook resulteerde in betere klinische uitkomsten. Het is verder belangrijk om op te merken dat, hoewel 50% van de episoden met APP werden gestopt, de andere 50% van de APP episoden werden voortgezet. Deze voortzetting van APP kan duiden op weerstand van behandelend artsen om zich te confirmeren aan behandelrichtlijnen en APP te verminderen, maar kan er ook op wijzen dat sommige patiënten baat hebben gehad bij APP en de combinatie daarom niet wordt gestopt (Tiihonen et al., 2019; Lahteenvuo and Tiihonen, 2021; Bighelli et al., 2022).

Bij de in hoofdstuk 4 beschreven studie hebben we ook prospectief onderzoek gedaan naar de redenen van behandelend artsen bij het starten en voortzetten van APP, waarvan we de resultaten hebben beschreven in **hoofdstuk 5**. Hoewel indicaties voor het toepassen van APP eerder zijn onderzocht in cross-sectionele studies, zijn er nauwelijks prospectieve onderzoeken naar de initiële indicaties voor APP en het verloop hiervan, zoals wij in deze studie hebben gedaan. Wij vonden dat APP voornamelijk werd geïnitieerd om te switchen naar een ander antipsychoticum, in mindere mate om agitatie en/of slaapproblemen te verminderen of om refractaire psychotische symptomen te behandelen. Dit is anders dan de resultaten van eerdere cross-sectionele studies, die vonden dat APP meestal werd toegepast voor de behandeling van refractaire psychotische symptomen (Gallego et al., 2012; Sernyak and Rosenheck, 2004). Bij 60 dagen follow-up van de indicaties bij deze patiënten vonden we dat APP bij ongeveer 50% was gestaakt. Hoewel de meeste indicaties voor voortgezette APP bij aanvang hetzelfde waren als bij follow-up, vonden we dat bij 29% van de patiënten die gestart waren met APP voor het kruislings switchen van antipsychotica de switch niet werd voltooid en de patiënt en voorschrijver “gevangen” zaten in cross-titratie, wat resulteerde in onbedoelde en mogelijk onnodige voortgezette APP.

Gezien de wisselende resultaten van klinische studies en de controversiële resultaten van meta-analyses over de werkzaamheid van APP zoals samengevat in hoofdstuk 3, de resultaten van afbouwstudies waarbij APP geleidelijk wordt omgezet in antipsychotische monotherapie (Bighelli et al., 2022), en nieuw bewijs over de effectiviteit van APP uit grote landelijke observationele studies (Tiihonen et al., 2019; Lahteenvuo and Tiihonen, 2021), onderzochten wij de hypothese dat er subgroepen patiënten zijn die baat kunnen hebben bij APP. Daarvoor deden wij de eerste meta-analyse van individuele patiëntdata (IPDMA) van 10 studies

met 602 patiënten met schizofreniespectrumstoornissen om kenmerken te identificeren van diegenen die baat hebben bij APP. De resultaten van deze studie worden gerapporteerd in **hoofdstuk 6**. We vonden dat de werkzaamheid van APP vergeleken met antipsychotische monotherapie afhangt van de ernst van de psychotische episode. APP is effectiever dan monotherapie bij patiënten met hoge PANSS-totaalscores en met overwegend positieve symptomen. Extrapiramidale bijwerkingen namen echter significant toe wanneer een eerste-generatie antipsychoticum werd gecombineerd met een tweede-generatie antipsychoticum. Het potentieel gunstige effect van APP op psychotische symptomen moet dus zorgvuldig worden afgewogen tegen het risico op meer bijwerkingen.

Algemene conclusies

Antipsychotische polyfarmacie (APP) bestaat tot op heden uit het combineren van twee antipsychotica, die beide primair werken door blokkade van de striatale postsynaptische D_2 receptor. Dit is dus een vorm van *same-class* polyfarmacie. Het bewijs voor de werkzaamheid en veiligheid van APP uit de systematische reviews en meta-analyses die we hebben beoordeeld is zwak en niet overtuigend. Wij hebben aangetoond dat gepersonaliseerde, op richtlijnen gebaseerde e-mailinstructie naar artsen potentieel onnodige APP kan verminderen. Ook hebben we aangetoond dat het kruislings omzetten van antipsychotica een risico inhoudt voor het ontstaan van mogelijk onnodige, persisterende APP als een patiënt verbetert tijdens deze omzetting en de omzetting daarom niet wordt voltooid. Dit wordt ook wel de *cross-titration trap* genoemd. Tot slot hebben we aangetoond dat er een subgroep van patiënten is die baat kan hebben bij APP. Deze subgroep bestaat uit patiënten met ernstige psychotische verschijnselen en overwegend positieve symptomen. Uit onze data konden we niet vaststellen welke combinaties van antipsychotica het meest effectief zijn en wat het mogelijke werkingsmechanisme is. Gezien de bewezen effectiviteit van clozapine bij patiënten met therapieresistente psychotische symptomen is het belangrijk dat eerst behandeling met clozapine wordt geprobeerd voordat APP wordt toegepast. Deze bevindingen kunnen APP een duidelijkere positie geven in toekomstige richtlijnen voor de behandeling van patiënten met ernstige psychotische stoornissen, met name op het gebied van symptoom reductie.

Aanbevelingen

Uit deze wetenschappelijke studie komen twee belangrijke aanbevelingen voort:

1. APP kan een gunstig effect hebben op het verminderen van psychopathologie bij ernstig zieke psychotische patiënten met overwegend positieve symptomen die onvoldoende hebben gereageerd op behandeling met clozapine. Deze informatie komt voort uit een IPDMA en is het hoogste bewijs dat momenteel beschikbaar is. Het is belangrijk dat deze kennis beschikbaar wordt gesteld aan behandelaars van patiënten met therapieresistente psychotische stoornissen door deze op te nemen in toekomstige updates van richtlijnen voor de behandeling van patiënten met psychotische stoornissen.
2. Geleidelijk kruislings overstappen van het ene op het andere antipsychoticum is een belangrijke risicofactor voor het ontstaan van mogelijk onnodige persisterende APP. Het optimaal omzetten van antipsychotica is nog onvoldoende onderzocht, maar moet worden afgestemd op de behoeften van de patiënt en op de eigenschappen van de betrokken antipsychotica. Overwogen moet worden of een onmiddellijke afbouw van het primaire antipsychoticum mogelijk is om deze vorm van APP te voorkomen.

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Als buiten-promovendus had ik geen contract bij de universiteit en was aangewezen op de coulance van mijn werkgevers en op mijn eigen vrije tijd om onderzoek te doen. Ik ben daarom de directie van de Rooyse Wissel in Oostrum (destijds Toine de Beer en Sanne Verwaaijen; thans Hyacinthe van Bussel), van de toenmalige GGz Nijmegen (Tom Kuipers en Jan van Haandel) en later de Raad van Bestuur van Pro Persona (destijds Christoph Hrachovec, Ron Akkerman en Cecile Exterkate; thans Patricia Esveld en Marc Verbraak) veel dank verschuldigd voor de uren die ik geruime tijd binnen werktijd in mijn onderzoek mocht investeren. Dat dit na verloop van tijd werd afgebouwd en gestopt is begrijpelijk gezien de lange tijdsduur van het traject. De tijd die ik zo gekregen heb heeft mij de ruimte gegeven een grondige basis te leggen en belangrijke mensen te betrekken, mede waardoor dit proefschrift tot stand is gekomen.

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*

Curriculum Vitae

Marc Lochmann van Bennekom (1958) was born in Venlo. After graduating from high school (Atheneum) at the St. Thomascollege in Venlo in 1977 and completing his medical studies at the Katholieke Universiteit Nijmegen (now: Radboud University), he did his alternative military service as a doctor in the psychiatric unit of the Merwede Hospital in Dordrecht. After working for a year as a doctor at the admissions department of the Psychiatric Hospital Wolfheze (now: Pro Persona Wolfheze), he became a resident in psychiatry at the St. Radboud University Hospital in Nijmegen in 1990. After registering as a psychiatrist in 1995, he worked at the admissions department of the Psychiatric Center Nijmegen (now: Pro Persona Nijmegen). In 2000, he accepted a job at the Forensic Psychiatric Center de Rooyse Wissel in Oostrum. In 2006 he returned to Pro Persona Nijmegen, where he worked at the outpatient clinic. Because of his interest in patients with severe mental illness, in 2008 he and his colleagues founded a specialized outpatient clinic for the treatment of patients with psychotic disorders, currently known as FACT-Vroege Interventie Psychose (Flexible Assertive Community Treatment team for early intervention in psychosis). A few years later, in 2010, in collaboration with his colleagues, he developed a specialized outpatient clinic for the treatment of patients with bipolar disorder, where he has enjoyed working ever since.

In 2011, he was appointed Director of Pro Persona's Bipolar Disorder Care Program, a position he held until Pro Persona's organizational structure was reorganized in 2022. Since then, he has served as chair of Pro Persona's Knowledge Network for Bipolar Disorders.

In addition to this thesis on antipsychotic polypharmacy in psychotic disorders, over the past 15 years his expertise and research have gradually expanded into the field of patients with bipolar disorder, with a particular focus on the early recognition of bipolar disorder and the treatment of bipolar depression. He has given several talks and (co-)authored several articles on the subject.

He is a member of the International Early Psychosis Association (IEPA), the International Society for Bipolar Disorders (ISBD), and the Dutch Knowledge Center for Bipolar Disorders (KenBiS), where he has chaired the Early Recognition Bipolar Disorders Working Group since 2015.

List of Publications

Peer reviewed

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- **Marc W.H. Lochmann van Bennekom**, Harm J. Gijsman, Joanna IntHout, and Robbert Jan Verkes Antipsychotic polypharmacy in time course: evidence for a cross-titration trap. J Clin Psychopharmacol. 2024 Nov - Dec;44(6):545-550 DOI: 10.1097/JCP.0000000000001916
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- Rosalie Beekman, Willemijn Bedaux, **Marc Lochmann van Bennekom**, Judith Bisscheroux, Manon Hillegers & Eline Regeer. Het belang van tijdige herkenning van bipolaire stemmingsstoornissen. Huisarts en wetenschap 2014, volume 67,38–41

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2007

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1992

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2016

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2012

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Voordrachten

2023

- Ketamine bij de bipolaire depressie (i.s.m. Ralph Kupka [Amsterdam UMC], Jeanine Kamphuis [UMC Groningen], Max de Leeuw [Leids UMC], Jasper van Zantvoord [Amsterdam UMC]). Symposium voorjaarscongres NVvP, 29 maart 2023, Maastricht

2022

- Vroegherkenning bipolaire stoornis en hoogrisico populaties (i.s.m. Manon Hillegers, Esther Mesman [Erasmus MC] en Eline Regeer [Altrecht]). Workshop voorjaarscongres NVvP, 22 mei 2022, Maastricht

2020

- Precisie diagnostiek van vroege stadia van de bipolaire stoornis bij adolescenten en volwassenen. E-Workshop, 48e digitaal voorjaarscongres NVvP, 17 juni 2020

2019

- Op weg naar een betere herkenning van bipolaire stoornissen in de toekomst – noodzaak en adviezen voor de klinische praktijk. Symposium 47e voorjaarscongres NVvP, 3 april 2019, Maastricht

2018

- (Vroege) interventies bij de bipolaire stoornis in translationeel perspectief: vanuit 'wetenschappelijk' risicoprofiel of 'eigen' veerkracht? Discussiegroep 46e voorjaarscongres NVvP, 13 april 2018 Maastricht

2017

- Behandeling van bipolaire stoornis: vanuit veerkracht of risicoprofiel? Discussiegroep 45e voorjaarscongres NVvP, 7 april 2017 Maastricht

2016

- Stagering en profilering van bipolaire stoornissen: implicaties voor de klinische praktijk. Refereerbijeenkomst Specialistisch Centrum Bipolaire Stoornissen Dimence, 21 juni 2016, Deventer
- Bipolaire depressie. Workshop op NijCa²re symposium "Behandeling complexe angst- en stemmingsstoornissen 2.0: Innovatieve visies voor de klinische praktijk." 21 april 2016, Nijmegen

2015

- Antipsychotische polyfarmacie in de klinische praktijk: zin of onzin? Voordracht Netwerk Geneesmiddelencommissies in de GGZ, 23 september 2015, Amersfoort
- Maatwerk bij de bipolaire stoornis: is vroegtijdige herkenning mogelijk en is het dan zinvol eerder te behandelen? Symposium 43e voorjaarscongres NVvP, 31 maart 2015, Maastricht
- (Ir)rationele antipsychotische polyfarmacie bij psychotische stoornissen: is er evidentie voor maatwerk? 43e voorjaarscongres NVvP, 31 maart 2015, Maastricht
- Bipolaire stoornissen in de basis GGz, geaccrediteerde nascholing voor verpleegkundigen Indigo Gelderland, 20 januari 2015, Pro Persona, Wolfheze (i.s.m. K. Feddema, SPV Pro Persona Arnhem)

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2014

- Vroege herkenning en interventies bij bipolaire stoornissen, voordracht Nascholing Psychiatrie Nijmegen, 19 november 2014, Nijmegen

2013

- Bipolaire stoornissen in de DSM 5. Waar komen we vandaan… en waar gaan we naar toe? Nascholingsmiddag DSM 5, 11 juni 2013, Pro Persona Wolfheze
- Zorgprogramma bipolaire stoornissen Pro Persona: focus op vroege interventie en functioneel herstel. Klinisch wetenschappelijke vergadering Kenniscentrum bipolaire stoornissen (KenBiS), 7 juni 2013, Pro Persona Wolfheze

2011

- Polyfarmacie in de psychiatrie. Nascholingssymposium Psychiatrisch Genootschap voor Nascholing Psychiatrie in Brabant, 18 november 2011, GGz Breburg, Etten-Leur (i.s.m. M. van Soest, apotheker ZALV)
- Over de spanning tussen richtlijn en patiëntsensitieve farmacotherapie bij de eerste psychose. Switchen van antipsychoticum en het risico op antipsychotische polyfarmacie Workshop 39e Voorjaarscongres Nederlandse Vereniging voor Psychiatrie, 31 maart 2011, Amsterdam (i.s.m. H. Gijsman en B. Jacobsen, psychiaters Pro Persona Nijmegen)

2010

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- Van richtlijn naar praktijk. Op weg naar een zorgprogramma bipolaire stoornissen voor Pro Persona. Referaat de Gelderse Roos (thans: Pro Persona), 9 november 2010, Wolfheze
- Farmacotherapie bij psychotische stoornissen na 2009: Back to the future? Referaat Nascholing Psychiatrie Nijmegen, 13 januari 2010, Nijmegen

2009

- Polyfarmacie in de psychiatrie: rationeel of irrationeel? Referaat APZ de Grote Rivieren, 10 februari 2009, Alblasserdam

2008

- Evidence based farmacotherapie bij een eerste psychose: preventie van polyfarmacie en medicatieontrouw. Workshop 36e Voorjaarscongres Nederlandse Vereniging voor Psychiatrie, 9 april 2008, Amsterdam

2007

- Polyfarmacie in de psychiatrie: rationeel of irrationeel? Onderzoekspresentatie 35e Voorjaarscongres NVvP, 12 april 2007, Maastricht

2000

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Posterpresentaties

2024

- Hanssen I, Ten Klooster P, Huijbers M, **Lochmann van Bennekom M**, Boere E, El Filali E, Geerling B, Goossens P, Kupka R, Speckens A, Regeer E. Development and validation of a Manic Thought Inventory. Poster presentation at the annual conference of the International Association for Bipolar Disorders, 29 september t/m 2 oktober 2024, Reykjavik, IJsland
- Lichtendonk P, Geerling B, Kupka R, **Lochmann van Bennekom M**, Regeer E. Triadisch perspectief op herstel. Posterpresentatie Voorjaarscongres NVvP, 10 t/m 12 april 2024, Maastricht

2016

- P. van Leeuwen, B.G. Tiemens, B. Koekkoek, G.J.M. Hutschemaekers en **M.W.H. Lochmann van Bennekom**. De MDQ-NL niet geschikt als screeningsinstrument voor bipolaire stoornissen in de generalistische basis GGz. Posterpresentatie 44e Voorjaarscongres NVvP, 30 maart t/m 1 april 2016, Maastricht

1992

- Van Hoof JJM, Raaymakers TWM, **Lochmann van Bennekom MWH**, Raes BCM (1992). Additional measures to improve the effectiveness of electroconvulsive therapy (ECT). Poster presentation at the First European Symposium on ECT; abstract book p.34
- Van Hoof JJM, Raaymakers TWM, **Lochmann van Bennekom MWH** (1992). Wat te doen als conventionele elektroconvulsieve therapie (ECT) faalt? Samenvatting posterpresentatie 20e Voorjaarscongres Nederlandse Vereniging voor Psychiatrie; Tijdschrift voor Psychiatrie; 34: 214

PhD Portfolio

Courses related to this thesis

2024

Responsible Conduct of Research, Utrecht University (online cursus door Coursera)

2022

Basic Course for Clinical Investigators (Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers; BROK®-cursus), Examenbureau Medisch-Wetenschappelijk Onderzoeker (EMWO)

1998

Cursus Klinisch Onderzoek in de Psychiatrie (Corsendonck cursus), Stichting ter Bevordering van Klinisch Onderzoek in de Psychiatrie.

Presentations related to this thesis

2015

- Antipsychotische polyfarmacie in de klinische praktijk: zin of onzin? Voordracht Netwerk Geneesmiddelencommissies in de GGZ, 23 september 2015, Amersfoort
- (Ir)rationele antipsychotische polyfarmacie bij psychotische stoornissen: is er evidentie voor maatwerk? 43e voorjaarscongres NVvP, 31 maart 2015, Maastricht

2011

- Polyfarmacie in de psychiatrie. Nascholingssymposium Psychiatrisch Genootschap voor Nascholing Psychiatrie in Brabant, 18 november 2011, GGz Breburg, Etten-Leur (i.s.m. M. van Soest, apotheker ZALV)
- Over de spanning tussen richtlijn en patiëntsensitieve farmacotherapie bij de eerste psychose. Switchen van antipsychoticum en het risico op antipsychotische polyfarmacie Workshop 39e Voorjaarscongres Nederlandse Vereniging voor Psychiatrie, 31 maart 2011, Amsterdam (i.s.m. H. Gijsman en B. Jacobsen, psychiaters Pro Persona Nijmegen)

2010

- Van richtlijn naar patiëntsensitieve farmacotherapie bij de eerste psychose. Switchen van antipsychoticum en het risico op antipsychotische polyfarmacie. Workshop 38e voorjaarscongres Nederlandse Vereniging voor Psychiatrie, 14 april 2010, Maastricht
- Farmacotherapie bij psychotische stoornissen na 2009: Back to the future? Referaat Nascholing Psychiatrie Nijmegen, 13 januari 2010, Nijmegen.

2009

- Polyfarmacie in de psychiatrie: rationeel of irrationeel? Referaat de Grote Rivieren, 10 februari 2009, Alblasserdam

2008

- Evidence based farmacotherapie bij een eerste psychose: preventie van polyfarmacie en medicatieontrouw. Workshop 36e Voorjaarscongres Nederlandse Vereniging voor Psychiatrie, 9 april 2008, Amsterdam.

2007

- Polyfarmacie in de psychiatrie: rationeel of irrationeel? Onderzoekspresentatie 35e voorjaarscongres NVvP, 12 april 2007, Maastricht.

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Data Management Statement

Ethics and privacy

This thesis is based on the results of research involving human participants, e.g., prescribing physicians (Chapters 2, 4 and 5), and on existing anonymized patient data obtained from published papers (Chapter 6), conducted in accordance with relevant national and international legislation and regulations, guidelines, codes of conduct and Radboudumc policy. This work has not been funded by any organization. The study reported in Chapter 2 involved psychiatrists from several institutions in the Netherlands on a voluntary basis and did not require IRB approval. The Institutional Review Board of GGZ Nijmegen (now: Pro Persona Mental Health Care), The Netherlands, has approved the quality improvement studies reported in Chapters 4 and 5. Ethical approval for the original studies included in Chapter 6 was obtained by the original study investigators.

The privacy of the patients involved in the studies reported in Chapters 4 and 5 was warranted by the use of pseudonymized data that were provided by the hospital pharmacy. For chapter 4 and 5, data was used that was previously collected in the context of healthcare (prescription of medication). To ensure responsible reuse of healthcare data, specific informed consent procedures were followed that are aligned with applicable laws, regulations and the national Code of Conduct for Health Research. Because this was a study to improve the quality of physician prescribing according to current treatment guidelines for reuse was not applicable. The privacy of the patients involved in the study reported in Chapter 6 was warranted by the use of fully anonymous data that were obtained from the original investigators of the included publications. Informed consent from the patients enrolled in the original studies was obtained by the original study investigators.

Data collection and storage

Data for Chapter 2 was obtained through paper (hardcopy) questionnaires completed and returned by physicians. These hardcopies are stored in cabinets at the department of Pro Persona Research, Wolfheze, the Netherlands. Digitalized data is stored on a secure server at Pro Persona.

Pseudonymized data for Chapters 4 and 5 was obtained from the hospital pharmacy and is recorded in a Microsoft Excel file. This digital data and metadata is stored on a secure server at Pro Persona.

Anonymized individual patient data for Chapter 6 was obtained from the original investigators and is stored on a secure server at Pro Persona. The pooled data and metadata are stored on a secure server of the Radboud Data Repository.

All data will be saved for 15 years after termination of the study.

Data sharing according to the FAIR principles

Due to the very specific properties of the data that are very closely linked to the institution and the physicians associated with them, the data used in Chapters 2, 4, and 5 are not suitable for reuse. Pro Persona is responsible for the management of this data. The original trial data that we obtained for Chapter 6 remain the property of the institutions where the investigators were associated with. The pooled data that we used in this chapter is on request available for re-use and can be accessed via the Radboud Data Repository https://data.ru.nl/collections/ru/rumc/ipdmaapp_t0000249a_dsc_734.

Donders Graduate School

For a successful research Institute, it is vital to train the next generation of scientists. To achieve this goal, the Donders Institute for Brain, Cognition and Behaviour established the Donders Graduate School in 2009. The mission of the Donders Graduate School is to guide our graduates to become skilled academics who are equipped for a wide range of professions. To achieve this, we do our utmost to ensure that our PhD candidates receive support and supervision of the highest quality.

Since 2009, the Donders Graduate School has grown into a vibrant community of highly talented national and international PhD candidates, with over 500 PhD candidates enrolled. Their backgrounds cover a wide range of disciplines, from physics to psychology, medicine to psycholinguistics, and biology to artificial intelligence. Similarly, their interdisciplinary research covers genetic, molecular, and cellular processes at one end and computational, system-level neuroscience with cognitive and behavioural analysis at the other end. We ask all PhD candidates within the Donders Graduate School to publish their PhD thesis in de Donders Thesis Series. This series currently includes over 600 PhD theses from our PhD graduates and thereby provides a comprehensive overview of the diverse types of research performed at the Donders Institute. A complete overview of the Donders Thesis Series can be found on our website: https://www.ru.nl/donders/donders-series

The Donders Graduate School tracks the careers of our PhD graduates carefully. In general, the PhD graduates end up at high-quality positions in different sectors, for a complete overview see https://www.ru.nl/donders/destination-our-former-phd. A large proportion of our PhD alumni continue in academia (>50%). Most of them first work as a postdoc before growing into more senior research positions. They work at top institutes worldwide, such as University of Oxford, University of Cambridge, Stanford University, Princeton University, UCL London, MPI Leipzig, Karolinska Institute, UC Berkeley, EPFL Lausanne, and many others. In addition, a large group of PhD graduates continue in clinical positions, sometimes combining it with academic research. Clinical positions can be divided into medical doctors, for instance, in genetics, geriatrics, psychiatry, or neurology, and in psychologists, for instance as healthcare psychologist, clinical neuropsychologist, or clinical psychologist. Furthermore, there are PhD graduates who continue to work as researchers outside academia, for instance at non-profit or government organizations, or in pharmaceutical companies. There are also PhD graduates who work in education, such as teachers in high school, or as lecturers in higher education. Others continue in a wide range of positions, such as policy advisors,

project managers, consultants, data scientists, web- or software developers, business owners, regulatory affairs specialists, engineers, managers, or IT architects. As such, the career paths of Donders PhD graduates span a broad range of sectors and professions, but the common factor is that they almost all have become successful professionals.

For more information on the Donders Graduate School, as well as past and upcoming defences please visit: http://www.ru.nl/donders/graduate-school/phd/

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