REVIEW ARTICLE

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Benefits and Risks of Antipsychotic Polypharmacy

An Evidence-Based Review of the Literature

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Abstract

Combination antipsychotic prescription is an increasingly common practice in clinical psychiatry. This clinical practice is at odds with clinical guidelines promoting antipsychotic monotherapy. Moreover, there has been increased concern over the safety profile of atypical antipsychotics in the last 10–15 years. We reviewed the literature on antipsychotic combinations with a focus on safety and efficacy. Multiple electronic database searches were complemented by relevant bibliography cross-checking and expert discussions. The review showed a literature that is dominated by case reports and uncontrolled studies. Polypharmacy was unequally studied, with some recent combinations (i.e. clozapine and risperidone) being extensively, albeit inconclusively, studied and other more commonly used combinations (first- with second-generation agents) receiving little attention. From an evidence-based perspective, further trials of antipsychotic association of sufficient power to address safety issues are needed before recommending any antipsychotic combination. Particular weaknesses of the present literature are low number of participants, lack of adequate control of confounding variables, short duration of experimental follow-up and inadequate monitoring of potential adverse effects.

1. What is Polypharmacy?

Webster's dictionary tells us that polypharmacy is (a) the act or practice of prescribing *too many* medicines, and (b) a prescription made up of many medicines or ingredients.[1] These two definitions are closely reflected by the scientific literature: the first definition, describing the clinical situation where more drugs are prescribed than clinically warranted, is considered a highly questionable practice, given its iatrogenic potential.[2] The use of the latter definition is hindered by the arbitrary threshold for "many medicines" (three, five or even nine medications[3]). Additionally, it may be argued that sometimes patients need, and do benefit from, multiple medicines.

Polypharmacy is defined in the present paper by (a) – as described in clinical terms by Fulton and Allen[4] as "the use of medications that are not clinically indicated". We argue that this definition has a greater applicability and usefulness in informing clinical practice.

Moreover, we argue that evidence-based medicine (EBM) literature, by addressing efficacy and safety issues, is able to inform our answers as to what is or is not "clinically indicated"; thus, being an essential tool in research on polypharmacy. On the contrary, if we were to consider the relativistic position that all medications have an effect, and thus an indication (would it be for placebo effect, patient reassurance, responding to patient's or entourage's demands, etc.), the present paper's subject would be meaningless. It is, however, important to nuance our position by acknowledging that pharmacotherapy is a complex clinical field involving more than EBM proofs of efficacy or safety.

Because antipsychotics are prescribed for various conditions, we will generally limit our discussion to patients suffering from schizophrenia-spectrum disorders. Even if this classification is problematic, we will follow the majority of the literature and refer to clozapine, olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole, sertindole, zotepine and amisulpride as second-generation antipsychotics. All other antipsychotics are referred to as first-generation.

1.1 Clinical Guidelines of Monotherapy versus Clinical Practice of Antipsychotic Combinations

The review of clinical guidelines[5-7] reveals that antipsychotics are essentially recommended in monotherapy. Paradoxically, in clinical practice, concomitant use of antipsychotics is seen in 13–90% of patients.[8] The higher numbers were reported in Japan (90%) and other East-Asian countries (45%).[9] In the US, antipsychotic combination rates used to vary between 13% in outpatient clinics and 50% in inpatients.[10] A recent epidemiological study of 61 257 Veteran Affairs patients showed that the prevalence of concomitant antipsychotic prescription was 20.0%, 13.1% and 9.5% when defined by a >30-, >60- or >90-day overlap, respectively.[11] Another study found that, in a 1-year period, 57.7% of 796 patients were treated with a combination of antipsychotics for a prolonged period (>60-day overlap).[12] In this study, among concomitant antipsychotics, 74% of patients were being treated with both a first- and a second-generation agent, 18% were receiving two second-generation agents and 6% were receiving two first-generation agents. These rates might be lower in the research population or university specialized clinics; in the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study, antipsychotic combination was present in only 6% at baseline.[13]

Recent large epidemiological studies[14,15] have reported distinct trends of increased use of antipsychotic combination therapy; in one study of 31 435 Medicaid recipients, in the 40% prevalence of antipsychotic combination prescriptions (mean overlap duration = 149 days), a significant factor was increased prescription between 1998 and 2000.[14] Further evidence to support a growing 'epidemic' of antipsychotic combinations, Clark et al.[15] reported a quadrupling of the rate of antipsychotic combination use (from 5.7% to 24.3%) between 1995 and 1999, along with an increased use of second-generation agents (from 43% to 70%) over the same time period, in a moderate sample (n = 836) of Medicaid claimants with schizophrenia spectrum disorders.

1.2 Hazards of Antipsychotic Polypharmacy

The potential hazards of combining antipsychotics include additional adverse effects (e.g. sedation, hypotension, anticholinergic toxicity, worsening metabolic profile), loss of advantages of second-generation antipsychotics (e.g. increased risk of tardive dyskinesia when adding a first-generation agent and presence of metabolic adverse effects – the worse of both worlds), pharmacokinetic interactions and higher costs. Moreover, complex prescriptions decrease compliance; thus, exacerbating a clinical problem often encountered in patients with schizophrenia or other psychotic disorders.

Unfortunately, there are few systematic studies that address safety concerns over antipsychotic combination in controlled trials. A prospective cohort study of 88 patients showed that prescription of more than one antipsychotic was associated with a 2.46 relative risk of reduced survival at 10 years.[16] In a case-control study of 70 pairs of hospitalized patients, antipsychotic combined treatment was associated with a longer stay in hospital and a higher risk of adverse effects, while the clinical improvement scores were similar.[17]

Given that antipsychotic combination might be hazardous and is not supported by clinical guidelines, would it be clinically indicated? Or might it be more of a "dirty little secret" of clinicians, as suggested by a psychopharmacology expert?[18]

Our aim is to explore the available evidence on various combinations of antipsychotics, to determine if they represent polypharmacy (i.e. are not clinically indicated) in patients with schizophrenia spectrum disorders, from an EBM perspective. For this purpose, we will review the scientific evidence of efficacy and safety of antipsychotic combination treatments. In light of the growing knowledge of the serious metabolic adverse effects of second-generation antipsychotics, we will consider the safety issues as essential for the debate over antipsychotic polypharmacy.

2. Review Methodology

The authors performed a computerized literature search with the following words: 'schizophrenia' AND ('antipsychotic' OR 'neuroleptic') AND ('augmentation' OR 'polypharmacy' OR 'adjunctive treatment'). The search was performed using OvidWeb (Ovid Technologies Inc., New York, NY, USA) in four databases: MEDLINE, OldMedline, PsychInfo and EBM Reviews (including Cochrane Database), with results limited to human studies and English language. Performing this search on 23 August 2006, we obtained 494 entries. The vast majority of these results were 'false positive'; in most cases they explored using other classes of psychotropics in addition to antipsychotics (e.g. antidepressants for post-psychotic depression) or the treatment of adverse effects of antipsychotics or were unrelated to treating primarily psychotic disorders (e.g. antipsychotic augmentation of antidepressants).

The results were thus manually and independently reviewed by the first two authors in order to limit risks of selection bias, and we obtained 49 clinical studies reporting safety and/or efficacy data on the use of combinations of at least two antipsychotic drugs in humans. During this process, we identified several editorials and reviews of the literature on related subjects. The manual verification of bibliographies from these literature reviews uncovered 25 additional clinical trials related to antipsychotic combination treatments. We would like to thank the anonymous reviewer who pointed out an additional case series.[19]

The relevant papers were reviewed and summarized, and the studies grouped by the combination of antipsychotics studied and with emphasis on the level of evidence (i.e. stressing randomized controlled trial [RCT] results). Theoretical and pharmacological knowledge was also considered in studying the antipsychotic combinations and weighting the type of evidence sought (e.g. the adverse event of agranulocytosis needs a high number of subjects given its relative rarity, metabolic syndrome needs a longer follow-up and a thorough biochemical investigation, and extrapyramidal symptoms [EPS] are preferably followed with a reliable, objective scale).

For each antipsychotic combination reported in the literature, clinical targets and evidence level were compiled and scored on a scale from one to five regarding their efficacy and safety[20] (table I). Efficacy scores follow the levels of evidence commonly used in EBM research. The safety scores are not related to efficacy scores (i.e. adding them would not result in a meaningful score). They are

Table I. Safety and efficacy rating scales

Rating	Description
Safety rating	
1	Safe: improves or no additional AE
2	Mild AE, no severe AE reported
3	Moderate, additive AEs and/or very rare serious events expected
4	Rare but significant serious events reported or expected
5	Evidence of increased serious events
Efficacy rating	
1	Two or more DBRCTs supporting the treatment
2	One positive DBRCT or subgroups of several DBRCTs
3	One or more open, controlled studies or one subgroup of a DBRCT
4	Case series or case reports
5	No evidence of efficacy

AE = adverse effect; **DBRCT** = double-blind, randomized controlled trial.

based both on published evidence and pharmacological knowledge. In order to minimize subjective choices, this scoring was developed by consensual discussions of the authors of this review (including experienced clinicians treating mainly patients with schizophrenia, a young psychiatrist, a resident, senior researchers in schizophrenia and a psychopharmacology expert). It is noteworthy that efficacy scores do not take into account some important factors (e.g. has there been an adequate therapeutic trial including both duration and dose? Are adverse effects the rate-limiting factor? Could drug-drug interaction be compromising the response?). Therefore, the authors would like to stress the fact that this score is not intended for use in clinical practice, but for obtaining a global image of the present state of evidence-based knowledge.

In spite of the widespread clinical use of antipsychotic combination treatment, we identified only six RCTs exploring the subject.

3. Clozapine and Risperidone

Clozapine and risperidone was by far the most studied antipsychotic combination, with 50% of all available RCTs (three of six) and 188 patients included (table II). An 'historic' and troubling fact is that one of these RCTs, published in 2005,[21] was the first positive RCT ever supporting antipsychotic combination treatment.

Given that clozapine has broad-spectrum receptor activity, but a weak dopamine D_2 blockade, it was hypothesized that risperidone (a significantly stronger D_2-antagonist agent) could enhance the therapeutic effects of clozapine non-responders.[21] Risperidone was probably favoured over other D_2 antagonists because of its better EPS profile at dosages lower than 6 mg/day.[27]

The clinical relevance of this combination was recently reviewed by Kontaxakis et al.[28] and Mouaffak et al.[29] It is noteworthy that the first review was based on analysis of only two RCTs[21,23] (total n = 70). We will discuss here the additional information provided by the largest RCT on the subject[22] (n = 68).

In this larger trial,[22] patients were treated with clozapine for at least 12 weeks, at doses of 400 mg and higher, before enrolling in the study. No further clozapine dose changes were allowed during the study. Criteria for clozapine-resistance were restrictive: a Positive and Negative Syndrome Scale (PANSS) total score of at least 80, a Clinical Global Impression (CGI) of at least 4 and a Social and Occupational Functioning Assessment Scale (SOFAS) of 40 or less. The risperidone dosage was limited to a maximum of 3 mg/day. The mean risperidone dosage was of 2.85 ± 0.44 mg/day, which was significantly lower than that of the other two RCTs. As detailed in table I, an extensive battery of measures was used to determine efficacy (both from psychopathological, cognitive and functional perspectives) and adverse effects. The study recruited the greatest number of patients (n = 68), yet failed to show any positive effects from adding risperidone in this population of clozapine-resistant patients. On the contrary, a significantly worse performance on a cognitive measure (verbal working memory) was reported in the active treatment group, and slightly higher plasma fasting glucose levels. This latter finding was not correlated with more overt cases of diabetes mellitus in the short term. However, the aetiology of antipsychotic-induced diabetes is still not completely understood, and the observed increased glucose plasma levels might be an early sign of it. Unfortunately, the short duration of this study prevents us from drawing any firm

Table II. Risperidone-clozapine combination treatment controlled studies for clozapine resistance

Author (year)	N	Clozapine dosage (mg/day)	Plasma clozapine (ng/mL)	Risperidone dosage (mg/day)	Duration (wk)	Efficacy			Safety		
						Scz+	Scz−	other	screening	reported AEs	serious events
Double-blind randomized controlled trial											
Honer et al.[22] (2006)	68	487–494 ± 131–171	488–540; NS change in time	2.85 ± 0.44	8 + 18 OLe (n = 46)	NS NS	NS NS	Verbal working memory worse in risperidone; p = 0.02	ESRS, BAS, UKU, metabolic screen (no prolactin level), WBC	Higher fasting blood glucose in risperidone, all others NS	1 case NMS-like
Josiassen et al.[21] (2005)	40	528.8 ± 166.7	NS change in time	4.43 ± 1.5	12	+ only at 12wk	+ at 6 and 12wk	Total BPRS at 12wk only	SAS, WBC, 'full' biochemistry panel	SAS increasing in risperidone, 2 cases of akathisia at 6 mg/day of risperidone	None
Anil Yağcioğlu et al.[23] (2005)	30	515.6 ± 138.7 risperidone vs 414.3 ± 96.9 placebo; p = 0.05	NS change in time	5.1 ± 01.3	6	NS	NS	GAS, QLS, CDS, all NS	UKU, SAS, BAS, AIMS, metabolic screen including prolactin, WBC	Hyperprolactinaemia, sedation	None
Open-label trial											
Taylor et al.[24] (2001)	13	487 ± 179 (↓ during trial to 317)	NR	3.0 ± 1.2	4–28 (mean 12)			7/13 ↓20% total PANSS, 4/13 marked improvement on CGI	NR	1 case compulsive rubbing	NR
de Groot et al.[25] (2001)	12	NR	NR	5.3 ± 1.4	4	Nil	Nil	NR	NR	1 case orthostatic hypotension	NR
Henderson and Goff[26] (1996)	12	479 ± 121	NS	3.8 ± 1.4	4	10/12 ↓20% BPRS+	7/12 ↓20% BPRS−	5/12 ↓20% BPRS− depression	NR	4 mild akathisia, 5 sialorrhea, 1 fatigue	NR

AEs = adverse effects; **AIMS** = Abnormal Involuntary Movements Scale; **BAS** = Barnes Akathisia Scale; **BPRS** = Brief Psychiatric Rating Scale; **CDS** = Calgary Depression Scale; **CGI** = Clinical Global Impression; **ESRS** = Extrapyramidal Symptom Rating Scale; **GAS** = Global Assessment Scale; **NMS** = neuroleptic malignant syndrome; **NR** = not reported; **NS** = non-significant; **OLe** = open-label extension; **PANSS** = Positive and Negative Syndrome Scale; **QLS** = quality-of-life scale; **SAS** = Simpson-Angus Scale; **Scz+** = positive symptoms of schizophrenia; **Scz−** = negative symptoms of schizophrenia; **UKU** = UKU adverse effect rating scale; **WBC** = white blood cell count; ↓ indicates decrease; + indicates positive; − indicates negative.

conclusions on metabolic innocuousness of this combination. Additional safety considerations are related to long-term effects of hyperprolactinaemia (which is described in risperidone addition to clozapine studies *when* the prolactinaemia is measured[23,26]) and to risks of developing tardive dyskinesia.

It can be argued that risperidone addition needs more than 8 weeks to show benefits: in Josiassen et al.,[21] results were negative at 6 weeks, but positive at 12 weeks. While the Honer et al.[22] study does not exclude this possibility, it is noteworthy that the open-label extension study[22] of 18 weeks failed to show any significant benefit even though 46 patients finished this extended study, and placebo effects were expected to be higher in the open-label extension.

In addition to the controlled studies, we identified several case reports and case series[24,25,30-42] that reported positive effects on a variety of outcomes in 11 of 13 cases but also undesirable adverse effects, such as orthostatic hypotension, lightheadedness, oculogyric crises, neuroleptic malignant syndrome, agranulocytosis, neutropenia and exacerbation of hoarding behaviours.

In summary, although this combination has been extensively studied, proof of efficacy has been elusive. There is still significant uncertainty regarding long-term safety, notably regarding tardive dyskinesia and metabolic adverse effects.

4. Clozapine and Amisulpride

The combination of clozapine and amisulpride was studied in a double-blind RCT protocol[43] with the primary goal of reducing clozapine-induced hypersalivation. Accordingly, the 40 patients' inclusion criteria were clozapine treatment and at least moderate clozapine-induced hypersalivation, but not clozapine resistance. The sample showed slightly less initial psychotic symptoms (PANSS = 61 ± 13 and CGI severity = 4.8 ± 0.95), with some patients probably not fulfilling criteria of clozapine resistance. The amisulpride addition was effective in diminishing hypersalivation after 3 weeks of treatment, but failed to show any efficacy on primary psychotic symptoms. The adverse effects profile was dominated by increased prolactinaemia in 95% of subjects. No extrapyramidal adverse effects were identified using the Simpson-Angus Scale (SAS) in this short term study.

This randomized, controlled trial did not confirm the previous positive case reports of amisulpride augmentation of clozapine.[44-46] Other studies have suggested that addition of amisulpride allows the clozapine dosage to the reduced, thus alleviating adverse effects such as sedation, hypersalivation or weight gain.[47-49]

The largest support for efficacy of the combination comes from an open study of 33 patients with suboptimal response to clozapine treatment.[50] A total of 28 subjects completed the 6-month study, showing statistically significant improvements on PANSS, Scale of the Assessment of Negative Symptoms (SANS) and Global Assessment Scale (GAS).

Given the significant shortcomings of the double-blind RCT[43] and the multiple positive open studies, amisulpride might be an effective adjuvant of clozapine therapy. In spite of reports of improved adverse effects, it is also clearly noted that hyperprolactinaemia is a significant common adverse effect of this combination.

5. Clozapine and Sulpiride

Given the low dopamine D_2/serotonin 5-HT_2 ratio of clozapine, the addition of a selective D_2 antagonist to clozapine has the potential to augment its antipsychotic activity. After the publication of two positive case reports,[51,52] sulpiride, which is a relatively selective D_2 antagonist, was studied by Shiloh et al.[53] in the only double-blind, RCT of first- and second-generation antipsychotic combination.[53] A total of 28 partial responders to clozapine received sulpiride 600 mg/day for 10 weeks in addition to their clozapine regimen. The subjects included in this study exhibited a partial and unsatisfactory response to clozapine following at least 12 weeks of treatment at an adequate dose, as defined by Brief Psychiatric Rating Scale (BPRS) scores above 25 and the inability to function as an outpatient. Moreover, the 5 weeks preceding enrolment had to be characterized by a stable clinical state (change in BPRS score <5%). The efficacy was measured with BPRS, Scale of the Assessment of Positive Symp-

toms (SAPS), SANS and the Hamilton Depression Rating Scale (Ham-D). Safety was monitored with weekly white blood cell count (WBC) and a biochemistry work-up including prolactinaemia testing. Additional adverse effects were reported by the clinical personnel (all subjects were hospitalized during the study).

The study authors observed a significant ($p < 0.001$) difference in response on SANS, but only trends for SAPS and BPRS. However, additional exploration of response to treatment (i.e. >20% reduction of symptoms) showed significantly ($p < 0.02$) more BPRS responders in the active treatment group (50% vs 8.3%). These results were paired by similar trends on the other scales, except for an absence of change for Ham-D. No severe adverse effects were reported. In the active treatment group, one patient developed clozapine-induced hypersalivation, another had an exacerbation of tardive dyskinesia and prolactin levels were increased 4- to 7-fold. Clozapine levels were not monitored; thus, a pharmacokinetic interaction leading to increased clozapine levels cannot be excluded as a potential explanation for these results. Moreover, the population studied was highly selective (i.e. clozapine non-responders and all patients receiving concomitant medications were excluded), limiting the generalization power of the study. Finally, the adverse effects profile was significantly worse in the active treatment group, and long-term effects were not assessed given the short duration of the trial.

Limited information is available on other antipsychotic augmentation of clozapine: case reports of pimozide and olanzapine;[54,55] two case reports[56,57] and two open-label studies[58,59] of aripiprazole (showing some change in psychopathology in one case and an improvement in metabolic syndrome in the other); two case reports of ziprasidone;[60,61] two case series (11 and 9 subjects) for ziprasidone suggesting a lower clozapine dosage, diminished positive symptoms and better adverse effects profile;[19,62] a case series of loxapine augmentation;[63] and three case reports of first-generation augmentation.[64]

6. Olanzapine and Sulpiride

Studies of clozapine and sulpiride combination seem to demonstrate a favourable response but with an important augmentation of adverse effects (see section 5). Raskin et al.[65] was the first to study a similar combination of olanzapine and sulpiride in an open-label, non-controlled, prospective trial. Olanzapine, which has a weak D_2/5-HT_2 ratio, was chosen because it is the atypical antipsychotic whose neurotransmitter receptor affinity profile most resembles clozapine. The advantages of olanzapine over clozapine include a better adverse effect profile (notably regarding life-threatening agranulocytosis and seizure risks) and greater ease of administration.[66] In the Raskin et al.[65] study, six patients (five diagnosed with chronic, treatment-resistant schizophrenia and one with acute psychosis but who had prior severe EPS with haloperidol and neuroleptic malignant syndrome after zuclopenthixol administration) received olanzapine (20–40 mg/day; mean = 27 mg/day) with an adjunction of sulpiride (377 mg/day) for 10–14 weeks. The authors reported an average decrease of 25 points (42.2%) in the BPRS score and 52 points (33%) in the PANSS score and a marked improvement on the CGI scale in all six patients. The time laps of response to the combination varied from 2 to 6 weeks (mean = 3.6 weeks), and no adverse effect was noted.

These encouraging results led Kotler et al.[67] to further explore this combination in a randomized study that included 17 patients diagnosed with chronic treatment-resistant schizophrenia (PANSS ≥70) who were receiving a stable dose regimen of olanzapine for at least 6 months before entering the study. Olanzapine dosage was fixed during the 8 weeks of the study, and placebo or sulpiride (titrated up to 600 mg/day by week 3 of the study) were added to olanzapine. The main objective of the study was to investigate any change in clinical symptoms and the adverse effect profile. Patients were rated at baseline and at 8 weeks by means of PANSS, Ham-D, Hamilton Anxiety Rating Scale (Ham-A), SAS, Barnes Akathisia Scale (BAS) and Body Mass Index (BMI). Sixteen (eight in the sulpiride group and eight in the control group) of the 17 patients completed the study. The only drop out was in the active group and was discharged from the treating unit

before the end of the study. Both groups were comparable regarding age, duration of illness, olanzapine dose and duration of olanzapine treatment as well as on baseline PANSS, Ham-D, Ham-A, SAS and BAS scores. The dose of olanzapine administered was 22.4 ± 4.37 mg/day. Statistical analysis of the results indicated no significant difference between the sulpiride augmentation group and the control group in the PANSS, Ham-A, SAS, BAS and BMI scores. However, the Ham-D scores indicated a significant improvement in the active group (−7.8 ± 3.6 vs −3.1 ± 5.1; $p < 0.05$). The authors specified that a trend improvement on PANSS negative subscale was obtained in the sulpiride group but the results did not reach statistical significance, possibly due to the small sample size (type II error). Therefore, this study than do not corroborate the uncontrolled findings of Raskin et al.[65] However, it is noteworthy that it demonstrates an improvement of depressive symptoms without significant additional adverse effects.[67] Limits of the study were the small sample size, the absence of double-blind, placebo-controlled study design and the absence of long-term follow-up.

7. Olanzapine and Risperidone

The olanzapine-risperidone combination was studied at a time when the first trials on combination clozapine-risperidone seemed to indicate its usefulness but raised the concern of possible associated severe adverse effects. There has been no randomized study on the combination of olanzapine-risperidone and only one open-label preliminary study to date.[68]

The study by Lerner et al.[68] included five hospitalized patients diagnosed with schizophrenia or schizoaffective disorder using the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV).[69] All patients received olanzapine or risperidone after failing to respond to several types of first-generation antipsychotics. After failure to this monotherapy, they were switched to the other atypical (risperidone or olanzapine) allowing cross-titration. During the switch of medication, there was a point at which any attempt to reduce the dose of either two drugs led to exacerbation of psychotic symptoms. Investigators noted the dosage corresponding to that point, assessed clinical status with BPRS at that point and compared it with baseline assessment results. The authors considered an improvement as clinically significant if there was a minimum 25% reduction in BPRS score. Complete blood counts were also performed during the study. The study authors observed an improvement in the positive symptoms in all patients and in the negative symptoms in one patient. Two of the five patients showed a marked improvement (31% and 38% on the BPRS), whereas the three others were considered as having a moderate improvement (25%, 27% and 29% on the BPRS). The olanzapine dosage varied from 10 to 15 mg/day and the risperidone dosage from 1 to 5 mg/day. There was no alteration in WBC and no adverse effect was registered. This preliminary study is in favour of the combination of olanzapine and risperidone but its small sample size and the absence of a control group limits its proof of efficacy.

Adding risperidone to a first-generation antipsychotic showed little benefit in ten subjects.[70]

8. Olanzapine and First-Generation Antipsychotics (Other than Sulpiride)

No RCTs have studied the combination of olanzapine and first-generation antipsychotics other than sulpride; however, one small, open-label trial from Mazeh et al.[71] reported improvement in three patients with schizophrenia partially responsive to monotherapy with olanzapine 20 mg/day. For 12 weeks, the researchers added a first-generation antipsychotic to the ongoing treatment with olanzapine. For each patient, a different classical antipsychotic was used according to its prior adverse effect profile: zuclopenthixol (60 mg/day), haloperidol (15 mg/day) and perphenazine (16 mg/day) were used. The authors reported a marked improvement in all three patients (as assessed with the CGI scale), a diminution of positive symptoms and no additional adverse effects.

In another case report, Takhar[72] reported that a 44-year-old man with chronic disorganized schizophrenia improved greatly with the combination of olanzapine 20 mg/day and pimozide 3 mg/day without added adverse effects. Before taking olanzapine, the patient's BPRS score was 65 and his Extrapyramidal Symptom Rating Scale (ESRS) score was 22, he had borderline tardive dyskinesia and scored

moderate on the Calgary Depression Scale (CDS). He was treated with olanzapine for 6 months, with limited improvement (BPRS decreased to 56, ESRS to 10, no tardive dyskinesia was noted and he scored mild on CDS). After a 7-week course of the combination treatment with pimozide, his BPRS improved to 38, his ESRS to 9, he still had no tardive dyskinesia and he was still scoring mild on CDS. His BMI remained unchanged.

In conclusion, these two studies are clearly limited by their uncontrolled design and sample size, but show no evidence that it might not be useful clinically to combine a first-generation antipsychotic to olanzapine in partial or non-responders.

9. Amisulpride and Other Second-Generation Antipsychotics

Amisulpride has a highly selective D_2/D_3 receptor antagonist activity and is supposed to improve negative symptoms at a low dose. It was argued that it might have a better adverse effect profile (no weight gain and less EPS) than first-generation antipsychotics.[73]

Lerner et al.,[74] in an open retrospective study, examined the records of 15 patients with resistant schizophrenia who were treated with amisulpride in combination with another second-generation antipsychotic (15 patients: five on clozapine 490.0 ± 174.6 mg/day, five on olanzapine 15.0 ± 5.0 mg/day, four on risperidone 6.0 ± 1.6 mg/day and one on ziprazidone 160 mg/day). The aim of the study was to evaluate the effectiveness and safety of these combinations. The mean dose of amisulpride was 693.3 ± 279.6 mg/day. The authors report that seven (46.7%) patients had a marked improvement, five (30%) patients had a mild improvement, three showed no improvement and none had a worsening of symptoms. In seven patients there was an amelioration of positive and negative symptoms including daily functioning. There was no difference in amelioration of symptoms between different combinations. Adverse effects were only seen in the risperidone-amisulpride group, where two patients had mild adverse effects (one light transitory tremor and one constipation).

This study suggests that coadministration of amisulpride and another second-generation antipsychotic might be effective and safe. Further prospective, controlled, double-blind and randomized studies using psychopathological scales are needed to confirm these results.

10. Haloperidol Augmentation

Two studies reported positive results with the adjunction of another antipsychotic to haloperidol. The first, a 2-month open-label trial by Bogetto et al.,[75] compared the efficacy of adjunction of fluoxetine or amisulpride to haloperidol on schizophrenic negative symptoms: 20 patients were randomly assigned to one of the two groups. An improvement of negative symptoms in both groups was observed but with a more rapid and more selective response in the amisulpride group. The authors also note that there was no increase of positive symptoms during the study.

In the second study, an 8-week, open-label trial, Higashima et al.,[76] studied the adjunction of the low-potency antipsychotic levomepromazine to haloperidol in acutely psychotic schizophrenic patients. Levomepromazine was chosen specifically because of its sedative properties, understood as complementary to the mainly incisive effect of haloperidol. A total of 19 patients were randomly assigned to monotherapy with haloperidol (ten patients) or to the combined therapy (nine patients). The authors reported that combination therapy was superior to monotherapy in the management of agitation.

11. Summary of Findings

We summarized the available evidence in table III and rated the evidence for safety and efficacy using the scale proposed by Tranulis et al.[20] and detailed in table I.

One may observe that no combination is supported by the highest level of evidence (i.e. replicated findings in randomized controlled designs) and level two evidence is limited to specific symptoms: negative symptoms for sulpiride-clozapine combination; moreover, this combination poses significant risks of non-serious adverse effects.

Combining risperidone and clozapine in clozapine-resistant patients is still a controversial issue after three double-blind RCTs and multiple uncon-

Table III. Safety and efficacy of antipsychotic combinations

Combination	Safety			Efficacy		
	AEs	serious events	rating	target symptoms	level of evidence	rating
Clozapine/risperidone	Sedation, EPS, hyperprolactinaemia, worse cognition, TD? metabolic syndrome?	Rare reports of NMS, agranulocytosis	4	Scz+ and Scz–	3 DBRCTs, mixed results (1 positive, 2 negatives)	3[a]
Clozapine/amisulpride	Hyperprolactinaemia; might reduce other AEs	None reported	3	Scz+ and Scz–	1 DBRCT (negative), 1 OL controlled trial (positive)	3
Clozapine/sulpiride	Hyperprolactinaemia, sialorrhea, worsening of TD	None reported	3	Scz–	1 DBRCT	2
				Scz+	1 DBRCT (trend only)	4
Clozapine/ziprasidone	Some AE improvement, additive sedation expected	None reported	3	Scz+/cognitive	Case series	4
Olanzapine/risperidone	None reported (small N), additive AE expected	None reported	3	BPRS	Case series	4
Olanzapine/amisulpride	None reported, additive AE expected	None reported	3	Scz+ and Scz–	Case series	4
Amisulpride/risperidone	EPS, constipation	None reported	3	Scz+ and Scz–	Case series	4
Haloperidol/amisulpride	Additive AE expected	None reported	3	Scz–	Control = antidepressant	3
Olanzapine/sulpiride	None reported, expected EPS and hyperprolactinaemia	None reported	3	Scz+	1 RCT (negative), 1 OL prospective trial (positive)	4[a]
				Scz–	1 RCT (trend), 1 OL prospective trial (positive)	4[a]
				Depressive	1 RCT	3
Olanzapine/other first-generations	None reported (small N), additive AE expected	None reported	3	CGI	Case series	4
Haloperidol/levomepromazine	None reported, mild additive AE expected	None reported	2	Agitation	OL controlled	3

a Mixed results with ongoing controversy over efficacy (see text for detailed analysis).

AEs = adverse effects; **BPRS** = Brief Psychiatric Rating Scale; **CGI** = Clinical Global Impression; **DBRCT** = double-blind, randomized, controlled trial; **EPS** = extrapyramidal symptoms; **N** = sample size; **NMS** = neuroleptic malignant syndrome; **OL** = open-label; **RCT** = randomized controlled trial; **Scz+** = positive symptoms; **Scz–** = negative symptoms; **TD** = tardive dyskinesia; **?** indicates questionable.

trolled studies. Our analysis emphasizes the safety risks of rare but potentially serious adverse effects and the lack of significant improvement when using moderate dosages of risperidone for a moderate but significant duration (8 weeks).

The scarcity of studies of antipsychotic combination is sobering. By comparison, bipolar disorders polypharmacy is much better studied: olanzapine and mood stabilizer combination studies have hundreds of patients in each group (e.g. one study had 344 patients enrolled,[77] more than all randomized studies of antipsychotic combinations together). Moreover, bipolar disorder clinical guidelines often support combination treatment in contrast with monotherapy-oriented schizophrenia guidelines.

One might consider the hypothesis that more research in antipsychotic combinations could also bring evidence in favour of using antipsychotic combinations. Although we cannot refute this hypothesis, it is more plausible that the lack of research is related to the scientific knowledge about the pathophysiology of schizophrenia. One may argue that the dopamine hypothesis and the fact that all antipsychotics have antidopaminergic activity influenced the vision of schizophrenia as a unidimensional illness: all therapies should aim at dopamine receptor blockade, hence only one drug should be used (and, as a corollary, psychotherapy is marginalized). French psychiatry advances an alternative view, where antipsychotics are classified based on several dimensions, one of the most common being the incisive-sedative dimension. According to this tradition, antipsychotics can be used in judicious combinations in order to obtain the desired mixed effect.[78]

Additional hypotheses regarding the scarcity of research focused on the clinically significant question of antipsychotic combination treatment concern a lack of financial interest from the industry and a lack of social and institutional pressure to improve standards of care for this stigmatized population. A reciprocal hypothesis is that clinicians' use of antipsychotic combinations is related to a desire to improve treatment outcomes and try to soothe the suffering of actively psychotic patients. However, one may wonder whether this well intentioned practice is a form of placebo treatment,[79] or a pragmatic reaction to the scarce research data.

This review of the literature has several shortcomings. A structural limitation concerns the nature of evidence-based literature: the absence of studies does not signify absence of knowledge on the topic. For example, basic science can predict pharmacological interactions, dangerous adverse effects or positive results. In this context, some clinical studies will never be performed because the benefit/risk ratio will simply not be favorable (e.g. combining clozapine and carbamazepine, because of increased agranulocytosis risk). In our study, we tried to incorporate this knowledge in our benefit and risk assessments (e.g. by using the term 'expected' adverse effects).

A second limitation is the risk of not retrieving all pertinent studies through our literature search. First of all, we had to limit our research, for practical reasons, to the Anglophone literature. We then might have neglected some pertinent studies published in other languages, notably given the previous discussion about France and some reports of a tendency to use multiple low-dose medications instead of a full-dose unique psychoactive substance in Asia (especially Japan). However, we were unlikely to miss important, high quality studies (which are generally published in Anglophone journals). Whenever additional studies were identified through cross-referencing, we incorporated them in our review as long as we were able to extract the safety and efficacy information. Furthermore, the used keywords returned a significant amount of false positive results, partly because no consensus exists on how to name the use of antipsychotic combination. It is thus possible that some studies were inadvertently rejected in the manual review. We tried to minimize this risk by having two authors review the studies independently and by reviewing the bibliographies of other recent reviews of the literature.

Finally, the little data available make any rating of safety and efficacy provisional and very sensitive to new information. Even for the best-studied combination (risperidone and clozapine), our rating can be radically changed by the results of only one new study. In this context, we strongly suggest that this review be interpreted with caution and that sound and nuanced clinical judgment is essential for translating these results into clinical practice.

12. Conclusion

The pervasive practice of antipsychotic combination treatment for patients with schizophrenia spectrum disorders is not supported by the EBM literature.

We are not advancing that antipsychotic combination therapy should be banished from clinical practice. Indeed, a good clinical practice implies taking into account multiple complex variables while determining the best clinical algorithm that should be followed for a given patient. However, it could be argued that, in light of a relative lack of research-supported proof of efficacy, a treatment using the combination of antipsychotics represents polypharmacy, i.e. the prescription of *too many* medicines from an EBM perspective.

Our literature review strongly suggests that further trials should explore various antipsychotic combinations. Sufficient power to address safety issues are needed before recommending any antipsychotic combination. Particular weaknesses of the present literature are low number of participants, lack of adequate control of confounding variables, short duration of experimental follow-up and inadequate monitoring of potential adverse effects.

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