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A translational research approach to poor treatment response in patients with schizophrenia: clozapine–antipsychotic polypharmacy

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Poor treatment response in patients with schizophrenia is an important clinical problem, and one possible strategy is concurrent treatment with more than one antipsychotic (polypharmacy). We analyzed the evidence base for this strategy using a translational research model focused on clozapine–antipsychotic polypharmacy (CAP). We considered 3 aspects of the existing knowledge base and translational research: the link between basic science and clinical studies of efficacy, the evidence for effectiveness in clinical research and the implications of research for the health care delivery system. Although a rationale for CAP can be developed from receptor pharmacology, there is little available preclinical research testing these concepts in animal models. Randomized clinical trials of CAP show minimal or no benefit for overall severity of symptoms. Most studies at the level of health services are limited to estimates of CAP prevalence and some suggestion of increased costs. Increasing use of antipsychotic polypharmacy in general may be a factor contributing to the underutilization of clozapine and long delays in initiating clozapine monotherapy. Translational research models can be applied to clinical questions such as the value of CAP. Better linkage between the components of translational research may improve the appropriate use of medications such as clozapine in psychiatric practice.

Introduction

The goal of the present paper was to use a translational research perspective to examine the strategy of antipsychotic polypharmacy for the clinical indication of poor treatment response in patients with schizophrenia. We examined the problem and related research using a “3T” model, as illustrated in Figure 1.¹ At each step of the pathway, knowledge informs the translational activity. The first knowledge area is basic science, forming an understanding of the pharmacology and mechanism of action of antipsychotic drugs from clinical research and animal studies. The available knowledge about

combining antipsychotic drugs should inform the first translational activity (T1): the key studies of antipsychotic polypharmacy strategies in patients. The results of this T1 translational activity then form the second knowledge area, an understanding of whether or not the antipsychotic polypharmacy strategy is efficacious. The next translational activity (T2) is an examination of which patients benefit (or experience side effects) from antipsychotic polypharmacy, which develops the third knowledge area related to clinical effectiveness. The final translational activity (T3) evaluates the cost of antipsychotic polypharmacy, with implications for the final goal of improved quality of health care.

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Basic science knowledge to inform translational research

The multitude of available antipsychotic drugs show a wide range of characteristics, including differences in receptor-binding profiles, extrapyramidal side effects and effects on behaviour in animal models.² The mechanism of action of virtually all approved antipsychotic medications is believed to require occupancy of the dopamine (DA) D2 receptor and antagonism of the effects of endogenous DA.^{3,4} However, about one-third of patients have a poor or limited response to antipsychotic drug treatment.⁵ The current best accepted strategy for these patients is to use clozapine, as this is the only drug shown to offer benefit to patients who have a poor response to adequate doses of other antipsychotic drugs.^{6,7} Despite this advantage, there are significant numbers of patients with a limited response to clozapine.⁸ In clinical practice, adding another antipsychotic drug to “augment” clozapine is common, occurring in as many as 60% of clozapine prescriptions.^{9–16} Combinations of antipsychotic drugs other than clozapine are also widely used clinically,^{17–20} with the perception that there are added benefits.^{21,22} This subgroup of patients, who may be refractory but are not offered or are unwilling to accept a trial of clozapine, are considered in more detail in the final section of this paper. Finally, there is even some suggestion of antipsychotic polypharmacy being used as a first-line treatment approach.²³

Preclinical studies of antipsychotic drug combinations are sparse. Despite an impressive array of animal paradigms that are efficacious in detecting compounds with antipsychotic properties, there are no more than a handful of reports on antipsychotic drug combinations. Preclinical models are used for numerous purposes. The most common are to detect the potential therapeutic properties of a drug or to understand the biological mechanisms through which the drug acts.²⁴ Animal models of the side effects of antipsychotic drugs have also received increased attention recently. For the former goal of therapeutic identification, a wide range of rodent paradigms is used. Most of these models measure the capacity of a drug to reverse behavioural alterations induced by experimental manipulation. Examples include inhibition of the locomotor effects of DA agonists, suppression of a conditioned avoidance response (CAR) and reversal of sensorimotor gating deficits.²⁴ Whereas these and other models have been in-

strumental in the development of novel antipsychotic drugs and elucidating their mechanism of action, such models all have inherent limitations. For example, current animal paradigms often emphasize predictive validity, whereby the capacity of the model to respond selectively to known antipsychotic drugs provides the confidence that they will respond likewise in response to future challenges. In the case of antipsychotic polypharmacy, where the human clinical data are controversial and preclinical data almost nonexistent, the justification for use of predictive validity alone is therefore questionable. Acceptable paradigms will be required to include additional forms of validity such as construct validity, which in turn requires the development of accurate constructs of the symptoms of schizophrenia.

One model that adequately meets the above criteria is the prepulse inhibition (PPI) of the acoustic startle reflex paradigm. The PPI translational model is based on widely-reported sensorimotor gating deficits that are noted in patients with schizophrenia, which can be reversed by treatment with antipsychotic drugs.²⁵ Deficits in PPI in humans correlate with both positive and negative symptoms;²⁶ as such, PPI deficits in animal models represent a surrogate for the overall severity of the disorder as a whole, rather than one specific group of symptoms. The physiologic pathways and neuro-anatomical brain regions that regulate PPI correlate well with those known to contribute to psychosis, and the pharmacological actions of compounds that reverse PPI deficits include the major targets for antipsychotic drugs, such as the DA D2 receptor. Importantly, for practical purposes of measuring additive therapeutic effects of antipsychotic polypharmacy, this paradigm is sensitive, in a dose-dependent manner, to both the therapeutic properties of drugs (via measurement of PPI) and to extrapyramidal side effects (via measurement of impairment in the initial startle response); additionally, it has a large therapeutic index. The implication is that synergistic effects of antipsychotic drug–drug polypharmacy should be apparent and quantifiable in this model, although this clearly requires empirical determination.

A number of studies have examined the effects of combining an antipsychotic with other psychotherapeutic compounds in alternate preclinical models such as the CAR task to enhance antipsychotic-like activity, although none with clozapine. The cholinesterase inhibitor galantamine, but not donepezil, augmented the antipsychotic-like effects in this

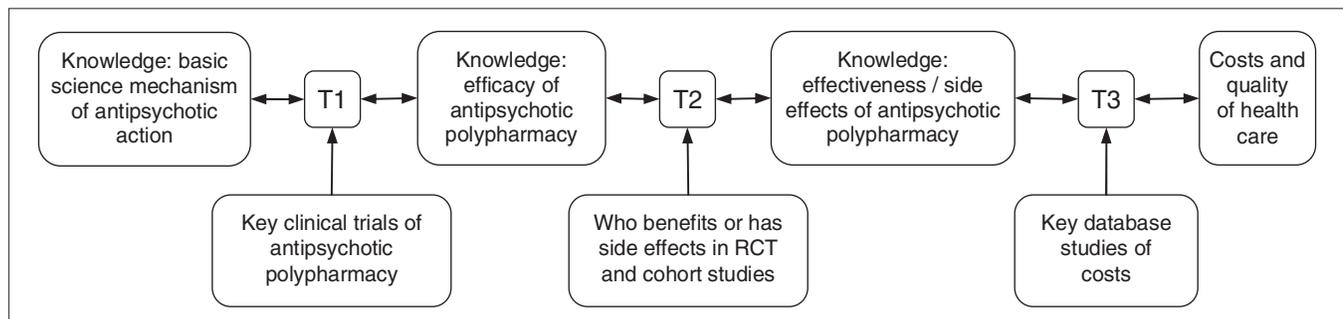


Fig. 1: Basic schema for applying a translational research approach to the problem of poor treatment response in schizophrenia, assessing the value of antipsychotic polypharmacy. This model is based on Dougherty and Conway.¹ RCT = randomized controlled trial.

task of the typical antipsychotic raclopride.²⁷ Similarly, the anticonvulsant drug topiramate also augmented the effects of raclopride in the CAR task without causing catalepsy.²⁸ The addition of the selective serotonin (5-HT) 2A receptor antagonist M100 907, a compound that has been ascribed antipsychotic properties,²⁹ to haloperidol increased antipsychotic-like responding in the CAR task,³⁰ but only over a narrow range. In the only study of 2 combined antipsychotic drugs, the atypical drug amperozide synergistically increased the effects of typical antipsychotics in the CAR task.³¹ Clearly, there is a need for more extensive preclinical study of antipsychotic polypharmacy combinations that are commonly seen in clinical practice, such as clozapine or olanzapine and risperidone. These experiments should employ additional models with high construct and pharmacological validity such as PPI procedures³² and use carefully titrated doses of drugs in a manner that will enable detection of putative synergistic effects.

There is also a paucity of preclinical data with respect to studies of the neurochemical effects of antipsychotic polypharmacy. The combination of an atypical antipsychotic with an antidepressant or mood stabilizer has been examined most commonly, although the direct relevance of these studies to antipsychotic activity remains unclear. For example, a well characterized property of atypical antipsychotic drugs is that they preferentially increase DA and acetylcholine efflux in the cortex and hippocampus relative to increases of these neurotransmitters in the nucleus accumbens.³³ In vivo cerebral microdialysis has been used to demonstrate that a low dose of the mood stabilizer divalproex potentiated DA, but not acetylcholine, release induced by olanzapine and aripiprazole in the medial prefrontal cortex and hippocampus.³⁴ Similarly, valproic acid potentiated cortical DA release by the atypical antipsychotics clozapine and risperidone as well as haloperidol,³⁵ whereas topiramate increased cortical DA release by raclopride without concomitant increases in the nucleus accumbens.²⁸ The combination of an antipsychotic with an antidepressant drug has generated less reliable findings, with one study reporting increased cortical DA release by coadministered fluvoxamine with olanzapine,³⁶ but no synergistic effect of either clozapine or risperidone with fluvoxamine on cortical acetylcholine release,³⁷ which would be predicted for enhanced antipsychotic activity. Although there do not appear to be studies of the effects of 2 combined antipsychotic drugs on DA or acetylcholine release, M100 907 increased the effects of haloperidol on cortical DA release while also inhibiting release of DA in the nucleus accumbens.³⁸ This latter effect is more consistent with an augmentation of atypical drug properties by haloperidol rather than enhanced antipsychotic activity per se.

One potential fruitful area for the preclinical study of antipsychotic polypharmacy is the side effects of antipsychotic drugs. Changes can potentially include those that are more closely associated with either typical or atypical antipsychotic drugs such as extrapyramidal symptoms versus metabolic side effects. Combinations of typical drugs, over a certain dose, would be expected to increase motoric side effects in most behavioural models; this remains to be determined empirically for nearly all drug combinations. Increased attention

to the metabolic side effects of atypical antipsychotic drugs has led to numerous homologous animal models. We have recently observed that there is a synergistic effect of a low dose of risperidone (1.0 mg/kg) on the glucose intolerance induced by a medium dose of clozapine (5.0 mg/kg) in rats, assessed by the glucose tolerance test (Barr and colleagues, unpublished observations, 2009). Interestingly, the addition of either ziprasidone or aripiprazole, both drugs associated with fewer metabolic side effects, decreased the hyperphagic properties of olanzapine in rats.³⁹

In summary, preclinical studies using a range of approaches such as the CAR task, PPI and glucose tolerance offer promise for understanding the possible mechanisms of action of combinations of antipsychotic drugs for either increased efficacy or increased side effects. Preclinical studies of combinations of other drugs with antipsychotics demonstrate the range of knowledge that can be obtained. In contrast, preclinical studies of combinations of antipsychotics are unfortunately too few to be informative.

Clinical research studies provide information concerning the possible mechanism of combining antipsychotic drugs.^{40,41} Even when used at high doses, clozapine may not occupy more than 65% of DA D2 receptors.⁴⁰ A positron emission tomography study indicated that the addition of a high potency D2 antagonist such as haloperidol to clozapine increased D2 receptor occupancy.⁴¹ Interestingly, the use of lower doses of clozapine in Europe compared with North America in the 1990s may have also been associated with greater use of clozapine–antipsychotic polypharmacy (CAP) in Europe.^{10,11,42} However, more recently, CAP appears to be increasing in North America^{15,16} and is a useful example to focus on for the translational research approach.

Translational research

T1. Knowledge concerning efficacy: studies of clozapine–antipsychotic polypharmacy

Clinical practice guidelines do not support CAP with a high level of certainty.^{43,44} However, clinicians may be increasingly challenged with patients having incomplete response to clozapine monotherapy and no compelling alternative treatment strategies.⁸ Although not addressing CAP specifically, surveys indicate that the main reasons for clinicians choosing antipsychotic polypharmacy relate to poor response of positive symptoms and poor behavioural control.^{21,22}

Risperidone is the antipsychotic drug investigated most thoroughly in combination with clozapine in randomized, placebo-controlled trials.^{45–49} The results of these studies are depicted in Figure 2. Although all groups of patients tended to improve in each study, there were no consistent effects related to risperidone or placebo augmentation. For the total severity of psychopathology, in 3 studies there was no statistical significance in the change over time in the placebo arm compared with the risperidone arm,^{45,47,49} 1 study favoured risperidone.⁴⁸

Other antipsychotic drugs were studied in combination with clozapine in randomized controlled trials (RCTs). No difference

from placebo was demonstrated for amisulpiride or aripiprazole,^{50,51} whereas sulpiride was slightly better than placebo in 1 study.⁴⁶ A head-to-head comparison of risperidone versus ziprasidone augmentation showed no difference between arms; however, there was no placebo supplementation comparison group.⁵²

There are several meta-analyses of CAP,^{53–57} and a recent meta-analysis of antipsychotic polypharmacy in general.⁵⁸ The more recent and comprehensive meta-analyses of CAP conclude that augmentation may have marginal benefits⁵³ or a modest to absent benefit.⁵⁴ The latter analysis noted that randomized, double-blind, placebo-controlled trials showed no advantage for antipsychotic augmentation of clozapine.⁵⁴ When lower-quality, open trials with no placebo arms were included in the analysis, an advantage for the addition of a second antipsychotic compared with clozapine alone was demonstrated. Overall, the authors “conclude that the evidence base supporting a second antipsychotic in addition to clozapine in partially responsive patients with schizophrenia is weak.” Both meta-analyses note that the effect size for CAP versus clozapine alone is likely to be small (0.1–0.2). In contrast, the effect size for typical antipsychotic to early clozapine treatment is estimated as moderate (0.4–0.5) and that for typical to optimal clozapine is large (0.8).^{7,59}

The authors of a meta-analysis of overall antipsychotic

polypharmacy reach a different conclusion: “In certain clinical situations, antipsychotic cotreatment may be superior to monotherapy.”⁵⁸ They do, however, note that the data on which this conclusion was based were subject to possible publication bias and were “too heterogeneous to derive firm clinical conclusions.” This analysis included 6 Chinese studies of augmentation of clozapine with risperidone or other antipsychotics, which contributed more than 50% weight to the analysis. We examined these studies in the original Chinese publications (E.Y.H.C.). Randomization was not described at all in 1 of the 6 studies and was described as “sequential” in 2 others. None had a placebo control. Only 1 of the 6 described blinding. The reporting of RCTs can be graded according to a standardized methodology, called the Jadad score.⁶⁰ This ranges from 0 to 5, with scores of 2 or lower indicating low-quality reporting. Of these 6 trials, 4 received Jadad scores of 1 in the analysis by Barbui and colleagues,⁵⁴ and 2 were not rated. In contrast, the 4 double-blind, placebo-controlled trials of risperidone augmentation described above received Jadad scores of 4 or 5. Whereas there is merit in trying to be as inclusive as possible when carrying out a meta-analysis, this must be balanced with the possible adverse consequences of including low-quality data. The data from high-quality studies on adding antipsychotic drugs to clozapine provide little or no support for this practice.

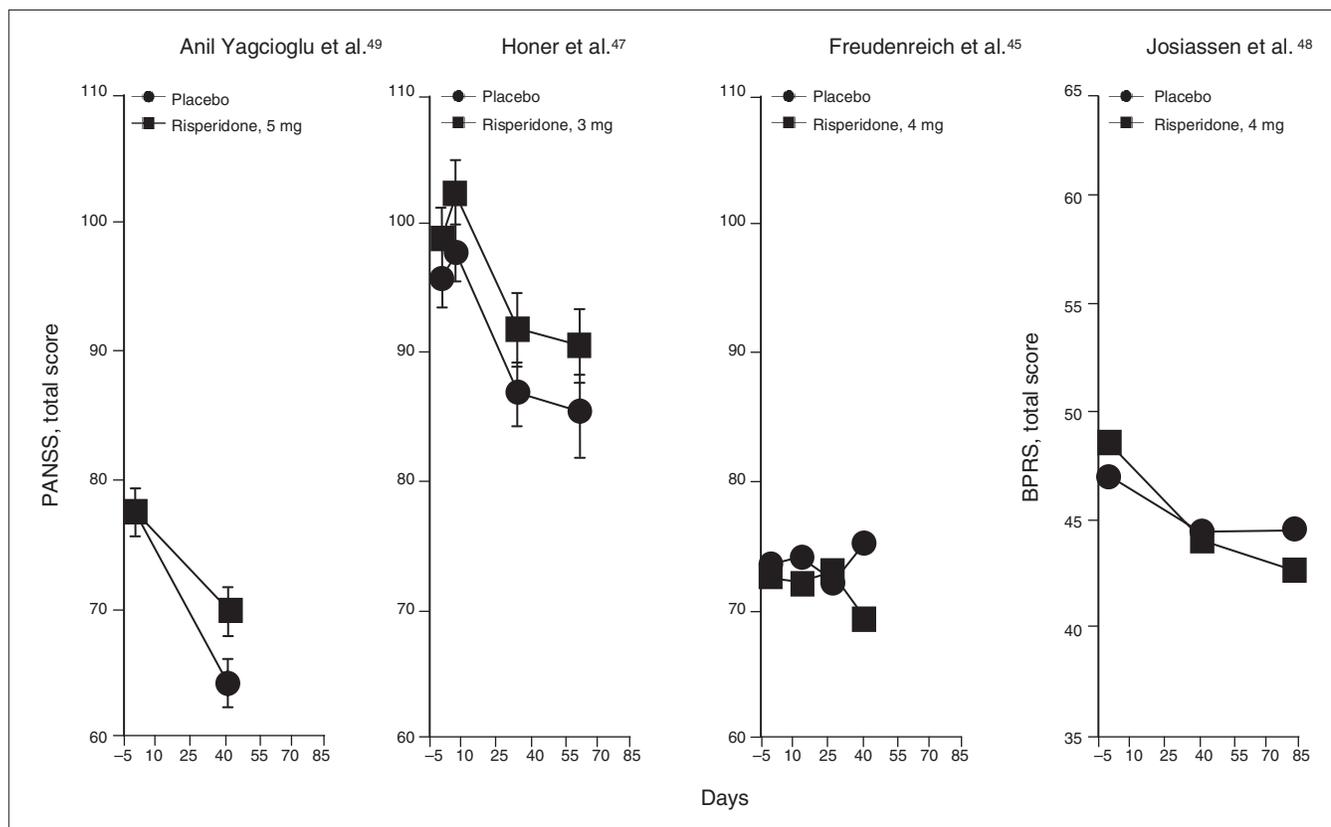


Fig. 2: Data redrawn from double-blind, placebo-controlled trials of risperidone augmentation of clozapine. The Brief Psychiatric Rating Scale (BPRS) total scores are plotted to be similar in range to the Positive and Negative Syndrome Scale (PANSS) scores, allowing comparison between studies. No consistent relation between improvement and type of augmentation (risperidone or placebo), baseline severity of illness or dose of risperidone was observed.

As described in the basic science section, there is more evidence for synergistic effects between antipsychotics and other psychotropic drugs than between combinations of antipsychotics. Clinically, general use of concomitant, mood stabilizing or other psychotropic medications along with antipsychotic drugs appears to be high, although studies of efficacy are limited.^{61–66} Based on the reported meta-analysis, anticonvulsant drugs such as lamotrigine may warrant further investigation, perhaps with novel designs targeting different features of illness than positive symptoms.^{67,68}

To this point, the basic science knowledge concerning antipsychotic polypharmacy does suggest that adding high potency antipsychotic drugs to clozapine will increase the occupancy of the DA D2 receptor. However, the clinical trials described in this section do not suggest substantial benefit from this strategy concerning efficacy. In this context, the next translational activity (T2) concerning the possible effectiveness of antipsychotic polypharmacy and CAP specifically needs to pay particular attention to side effects or possible harms.

T2. Knowledge concerning effectiveness and possible harms of antipsychotic polypharmacy and CAP

Despite lack of endorsement by clinical treatment guidelines, the practice of antipsychotic polypharmacy continues to increase.⁶⁹ A review of the literature finds that the overall point

prevalence of antipsychotic polypharmacy in general ranges anywhere from 4% to 69%.^{9,13–16,22,70–91} This wide range can be explained in part by differences in study design, patient population, diagnosis, coverage and treatment setting. An increase in the prevalence over time has also been reported in the literature.

In 3 studies that examined longitudinal prescribing trends in Medicaid recipients, antipsychotic polypharmacy increased from 6% in 1995 to 24% in 1999 ($n = 836$), from 32% in 1998 to 41% in 2000 ($n = 31\,435$) and from 3% in 1999 to 14% in 2004 ($n = 15\,962$).^{13,75,90} We have also reported an increase in antipsychotic polypharmacy at discharge in a tertiary care facility in British Columbia; in this case, the practice increased from 28% to 45% between 1996 and 2000.^{15,16} For those studies that reported data on clozapine, the point prevalence rates for CAP ranged from 11% (Medicaid claims) to 53% (tertiary care facility; Table 1).^{9,13–16,71,72,74} As with antipsychotic polypharmacy in general, we found a parallel increase in the prevalence of CAP over time in discharged prescriptions from a tertiary care facility increasing from 22% in 1996 to 53% in 2000.^{15,16}

Antipsychotic polypharmacy is reported to be associated with excessive dosing compared with monotherapy in inpatient and outpatient samples.^{9,92} Of particular interest in the outpatient study was that the dose for the individual antipsychotics increased when prescribed as part of a polypharmacy regimen. This observation fails to support a previously

Table 1: Summary of the prevalence of clozapine use and clozapine–antipsychotic polypharmacy

Study	Sample (no.)	Definition of polypharmacy	Period	Source	Location	Diagnoses	Clozapine treatment, %		
							Overall prevalence	Mono	CAP
Procysbyn et al. ¹⁵	Inpatients (229)	Antipsychotics at time of discharge from hospital	1996–1998	Pharmacy database	Canada	• Schizophrenia	22	78	22
Jaffe and Levine ⁷⁴	Inpatients (12 122)*	Antipsychotic ≥ 28 d	1999	Integrated research database	USA	• Schizophrenia • Schizoaffective disorder • Bipolar disorder • Major depression • Other	17	66	34
Taylor ⁷³	Inpatients (475)	Antipsychotic† on the day of chart review	2002	Chart review	UK	• Not specified	40	77	23
Procysbyn and Thompson ¹⁶	Inpatients (372)	Antipsychotic at time of discharge from hospital	2000	Pharmacy database	Canada	• Schizophrenia • Schizoaffective disorder • Bipolar disorder • Psychosis NOS	19	47	53
Ganguly et al. ¹³	Medicaid recipients (31 425)	Antipsychotic ≥ 61 d	1998–2000	Medicaid claims database	USA	• Schizophrenia	7	64	36
Kreyenbuhl et al. ⁷²	In- and outpatients (45 571)	Antipsychotic ≥ 90 d	2000	VA National Psychosis Registry	USA	• Schizophrenia • Schizoaffective disorder	3	79	21
Morrato et al. ¹⁴	Medicaid recipients (55 481)	Antipsychotic ≥ 60 d	1998–2003	Medicaid claims database	USA	• Schizophrenia • Bipolar disorder • Major depression	< 1	89	11
Broekema et al. ⁷¹	Inpatients (2 725)	Antipsychotic ≥ 6 wk	1998–1999	Pharmacy database	Multiple Europe	• None excluded	25	69	31
Procysbyn et al. ⁹	Outpatients (435)	Antipsychotic ≥ 90 d	2005–2006	Provincial data system	Canada	• Schizophrenia • Schizoaffective disorder • Bipolar disorder • Major depression • Psychosis NOS	8	73	27

CAP = clozapine–antipsychotic polypharmacy; mono = monotherapy; NOS = not otherwise specified.

*Prescribing episodes, that is, any episode of antipsychotic polypharmacy of at least 28 days during the study period. Patients may have experienced more than 1 prescribing episode during their hospital stays.

†Limited to clozapine or olanzapine.

proposed rationale for antipsychotic polypharmacy: that using lower dosages of 2 agents with different receptor and side effect profiles may achieve efficacy while mitigating side effects that would have occurred at a higher dosage of a single agent.⁷⁰ Also, the suggestion that practitioners may be prescribing small doses of a second antipsychotic to treat auxiliary symptoms such as sleep or anxiety is not substantiated by this data.

Adverse events associated with antipsychotics can be neurologic or non-neurologic. In general, the neurologic side effects are more often associated with high-potency agents such as those commonly used to augment clozapine. These side effects result from antagonizing DA D2 receptors in the nigrostriatum and include extrapyramidal symptoms (e.g., dystonias, parkinsonism, akathisia), tardive dyskinesia and the neuroleptic malignant syndrome. Non-neurologic side effects are more often associated with lower-potency antipsychotics (clozapine and others) and include sedation, orthostatic hypotension, QTc interval prolongation, central and peripheral anticholinergic effects, endocrine effects (e.g., galactorrhea, gynecomastia, amenorrhea), sexual dysfunction (e.g., diminished libido, retrograde ejaculation), photosensitivity, weight gain and agranulocytosis. Whereas some of these side effects are relatively benign, others contribute to increased morbidity and perhaps mortality. For example, antipsychotics that prolong the QTc interval may increase the risk of sudden death, particularly in individuals with pre-existing cardiac disease and those taking other QTc-prolonging medications.⁹³

The frequency and severity of these adverse events are relatively well established and documented for antipsychotics used as monotherapy. In contrast, there is relatively little literature regarding the rate of occurrence and severity of these and other adverse events (or for drug–drug interactions) that are associated with antipsychotic polypharmacy. As pointed out in several reviews, the antipsychotic polypharmacy literature relies much more on individual case reports.^{17,61,94} However, 2 epidemiological studies implicate antipsychotic polypharmacy in premature death.^{95,96}

Concerning CAP in particular, some of the known side effects of clozapine may be exacerbated by adding an additional antipsychotic drug, including sedation (clozapine/risperidone),⁴⁹ increased fasting glucose levels (clozapine/risperidone)⁴⁷ and hyperprolactinemia (clozapine/risperidone, clozapine/haloperidol, clozapine/sulpiride).^{41,46,97} Whereas exacerbation of extrapyramidal side effects is not reported in the RCTs of CAP using standardized ratings, worsening of extrapyramidal side effects is reported in individual patients in these and other studies.^{41,47,98} New side effects or consequences of CAP may include effects on cognitive function. Several types of cognitive tests, including those assessing memory, show improvements over time likely related to practice effects. Interestingly, in 2 RCTs, the addition of risperidone to clozapine appeared to block or improve these expected practice effects.^{47,99} The implications for cognitive function in everyday life are uncertain.

Whereas the knowledge concerning efficacy of CAP and antipsychotic polypharmacy provides no or only very limited support for the strategy, the translational studies of effective-

ness indicate that the possibility of side effects or possible harms may outweigh any benefits. The final phase of examination of antipsychotic polypharmacy as an attempt to treat refractory forms of schizophrenia needs to consider the costs to the health care system.

T3. Knowledge concerning costs and quality of health care

Apart from the suffering experienced by patients and family members, schizophrenia imposes a great economic burden on the health care system and society alike as a result of its prevalence, early onset and chronicity.^{100,101} The costs associated with schizophrenia can be divided into the direct costs of treatment and care, the indirect cost of lost productivity and caregiver time and the intangible costs of pain and suffering as a consequence of a reduction in quality of life. Although numerous studies have assessed the cost-effectiveness of antipsychotics, they are almost exclusively restricted to monotherapy.¹⁰² Furthermore, in many cases the reported outcomes are contradictory, thus making it difficult for policy-makers to generalize the findings and draw firm conclusions. Notwithstanding these limitations, the accumulated evidence would support the claim that clozapine monotherapy is cost-effective in treatment-refractory patients, primarily as a result of decreased costs of stays in hospital.^{103–105}

Data from a prospective multisite observation study were used to compare medication cost associated with antipsychotic polypharmacy for patients taking either olanzapine, risperidone or quetiapine monotherapy.¹⁰⁶ Expectedly, antipsychotic polypharmacy was found to substantially increase treatment costs compared with monotherapy, in some cases doubling the daily medication expenditure. This finding was corroborated in an RCT that allowed antipsychotic polypharmacy¹⁰⁷ and in studies using data from Medicaid claims from various jurisdictions (New Hampshire,⁹⁰ California and Georgia,¹³ California,¹⁰⁸ San Diego County,⁷⁵ and California, Nebraska, Oregon, Utah and Wyoming¹⁰⁹). Apart from drug acquisition costs, there are also data to suggest that antipsychotic polypharmacy is associated with higher rates of hospital admission⁷⁵ and longer lengths of stay in hospital.¹¹⁰ This is particularly relevant as hospital stays are the main driver of direct costs associated with the treatment of schizophrenia.¹¹¹ However, these retrospective studies cannot distinguish between the possibilities of more severe illness and consequences of antipsychotic polypharmacy. Finally, one must also consider the additional costs (both direct and indirect) expected to be associated with using multiple medications in general. These costs result from an increased incidence of adverse events, drug–drug interactions, medication error and nonadherence. The issue of nonadherence merits further comment, as it is the most consistent predictor of relapse in patients with schizophrenia and thus will significantly increase direct costs associated with health services, including hospital stays.^{101,112–117} Taken together, the added expense incurred with antipsychotic polypharmacy and the lack of evidence for this practice warrants further research to assess its cost-effectiveness. To date, no pharmacoeconomic studies exist for CAP.

The increasing prevalence of antipsychotic polypharmacy in general may conceal additional risks for the treatment of patients with refractory forms of schizophrenia. As many as one-third of patients might have poorly responsive forms of illness and could benefit from clozapine.⁵ Yet, in our recent outpatient study, the prevalence of clozapine utilization was far lower at slightly less than 8% (Fig. 3).⁹ Although clozapine can be initiated after poor response to 2 trials of antipsychotic medication, the delay between completing such trials and initiating clozapine is reported to be 5 years or more in 2 studies.^{118,119} In a British study, nearly two-thirds of these patients had a trial of antipsychotic polypharmacy before clozapine.¹¹⁹ Another study from the United States reached similar conclusions.²² Of interest, one report indicates that polypharmacy using medications other than clozapine can be reduced by the introduction of treatment with clozapine.¹²⁰

Conclusion

The preclinical knowledge base providing a rationale for CAP or other types of antipsychotic polypharmacy is not well developed. A very limited bridge from this approach to human studies is provided by a positron emission tomography study of haloperidol combined with clozapine. However, the quality of evidence supporting the efficacy of adding antipsychotic drugs to clozapine or of antipsychotic polypharmacy in general is poor, with the possible exception of studies of risperidone added to clozapine in which the benefit appears to be minimal or none. Clinical research in this area should continue to have a high priority until the gap between practice and evidence is narrowed.¹²¹ In terms of effectiveness, the side effects and possible harms related to antipsychotic polypharmacy in general and CAP in particular appear to outweigh any possible advantages. Despite the weak evidence base, prescribing behaviour assessed in service delivery systems continues to show wide use of CAP and other forms of antipsychotic polypharmacy and higher associated costs. The extent of antipsychotic polypharmacy in a health care system could even be considered as a possible marker of non-evidence based care.

These challenges to implementing a translational medicine strategy are not unique to CAP. At the T1 stage, preclinical

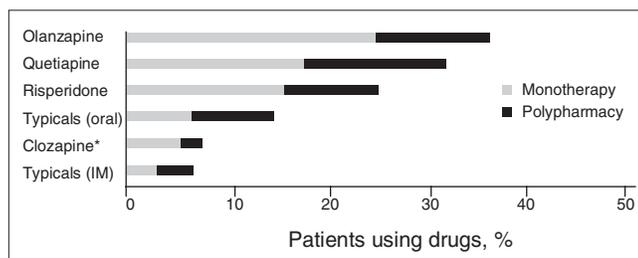


Fig. 3: Overall antipsychotic utilization in an outpatient sample of 435 patients with chronic mental illness cared for by community mental health teams in Vancouver, Canada.⁹ Clozapine utilization in this population is low, and overall, antipsychotic polypharmacy was substantial for each type of drug. IM = intramuscular; typical = typical antipsychotics.

models of human illness or of drug effects often have serious limitations. Even when research is available, the pathway from clinical discovery to application in medicine is often as long as 25 years.¹²² Translational medicine at the T1 stage could be improved by increasing emphasis on the possibilities of bidirectional studies. Clinical experience can be as valid a source of inspiration for basic research as the curiosity-driven approaches at the laboratory bench are for research on useful drugs for illness. Preclinical studies of CAP that focus on mechanism of action in the brain and studies concerning side effects would be of value.

At the T2 stage, examining the effectiveness of clozapine in the broader population and the contexts in which it is prescribed may help focus second iterations of efficacy studies. Similar considerations apply to dosing of antipsychotic medications in general, where patterns of clinician behaviour can diverge from the initial recommendations based on RCT studies.^{123,124} Assuming the efficacy data do translate into effectiveness, the steps involved may include expert consensus, incorporation into guidelines and uptake into quality assessment or performance measures, which can include financial incentives in some delivery systems.¹²⁵ More work in this area focused on CAP could have broader benefits for quality of care of patients with more severe schizophrenia.

To achieve the T3 goal of overall system improvement in cost-effective quality improvement, dissemination of knowledge is not enough.¹²⁶ More emphasis on moving “from a science of recommendation to a science of implementation” is needed.¹²⁷ Again, this need not be unidirectional, as population-based studies can provide valuable information to help shape research at the earlier phases of translation.¹²⁸

Overall, maintaining reciprocal connections between researchers at each T1–T2–T3 juncture is crucial,^{1,126} as is the flow of information back and forth between efficacy and effectiveness.¹²⁹ The need for broader use of clozapine and a more full understanding of the implications of CAP represent an excellent opportunity for an integrative translational research approach.

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Contributors: Drs. Honer, Procyshyn, Chen and Barr reviewed the literature. Drs. Honer, Procyshyn, Chen and Barr wrote the article; all authors read and revised the article. All authors gave final approval for the article to be published.

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