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Schizophrenia and related psychoses CHAPTER 1 monotherapy.²⁴ Although the interpretation of such real-world findings is hindered by the issue of confounding by indication,²⁵ there are perhaps several plausible explanations for improved efficacy with polypharmacy. It may be that combining antipsychotic medications with different receptor profiles can be more effective and lead to better therapeutic efficacy and/or a lower adverse-effect burden and therefore better outcomes. It may be also that co-prescribing two antipsychotic medications improves medication adherence in that it increases the likelihood that a patient may use at least one of them.²⁴ Notably, clozapine and LAI antipsychotic preparations appear to be the most effective monotherapies for relapse prevention in schizophrenia.²⁶ Thus, adding a second antipsychotic medication to clozapine or an LAI antipsychotic medication in an attempt to mitigate metabolic adverse effects (e.g. by adding aripiprazole) or manage symptoms of agitation, anxiety or sleep disturbance (e.g. by adding olanzapine or quetiapine) might enhance a patient's engagement in their treatment and improve adherence to the effective antipsychotic treatment that has been augmented. Adverse effects Evidence for possible harm with combined antipsychotic medications is perhaps more convincing. Clinically significant adverse effects have been associated with combined antipsychotic medications, which may partly reflect that polypharmacy regimens are commonly a high-dose prescription.^{8,27} There is an increased prevalence and severity of EPS,^{28,29} increased metabolic adverse effects and diabetes,^{22,30,31} sexual dysfunction,³² an increased risk of hip fracture,³³ paralytic ileus,³⁴ grand mal seizures,³⁵ prolonged QTc,³⁶ hypertension³⁷ and arrhythmias.¹³ Switching from antipsychotic polypharmacy to monotherapy has been shown to lead to worthwhile improvements in cognitive functioning.²⁰ The evidence relating to an increased mortality with a continuing antipsychotic polypharmacy regimen is inconsistent. Two large case-control studies and a database study³⁸⁻⁴⁰ found no increased mortality in patients with schizophrenia receiving antipsychotic polypharmacy compared with antipsychotic monotherapy. However, a 10-year prospective study of a cohort of 88 patients with schizophrenia found that receiving more than one antipsychotic medication concurrently was associated with substantially increased mortality.^{18,41} These investigators explored the possibility that the use of combined antipsychotic medications might be a proxy for greater severity/increased refractoriness of psychiatric illness but found no association between mortality and any measured index of illness severity, although these measures focused on negative symptoms and cognitive deficits. Further, analysis of data from a large anonymised mental healthcare database (2007-2014) of 10,945 adult patients with serious mental illness who had been prescribed a single antipsychotic or polypharmacy for 6 months or more revealed a weak association between regular, long-term antipsychotic polypharmacy and all-cause mortality and natural causes of death.⁴² However, the authors concluded that the evidence for the association was limited, even after controlling for the effect of dose. Another study,

involving the follow-up of 99 patients with schizophrenia over a 25-year period, found that those prescribed three antipsychotics simultaneously were twice as likely to die as those who had been prescribed only one.⁴³ These authors also considered the possibility of indication bias influencing the findings, speculating that combined antipsychotic medication might be more likely to be prescribed for the most severe schizophrenia.

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