Focus on Polypharmacy in schizophrenia: does anyone truly benefit?

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Dr Suzuki and colleagues (Suzuki et al., 2004) are to be commended for their contribution of a novel, systematic study of polypharmacy in schizophrenia – a surprisingly under-studied topic given its high prevalence worldwide. We find their results quite informative and agree with their thoughtful and very balanced discussion of their results.

What should we conclude based on their finding that roughly three-quarters of patients appear not to have benefited from polypharmacy? Should polypharmacy be abandoned? Alternatively, since Suzuki and colleagues failed to discern any net benefit from converting patients from polypharmacy to monotherapy, why should we care whether clinicians use a seemingly benign approach with minimal therapeutic impact?

We will briefly reiterate some of the issues already identified by Suzuki and colleagues that limit generalizations from their data to current clinical practice.

First, in Japan, at the time of this study, antipsychotic prescribing was almost exclusively limited to conventional agents, and as many as 90% of schizophrenia patients received more than one antipsychotic. This frequency and manner of combination therapy differs markedly from the current situation in most clinical settings. Secondly, open uncontrolled designs invariably raise concerns about the validity of results, since unintended biases may influence outcomes, and outcomes may be misattributed to the intervention under study (the switch from polypharmacy to monotherapy) rather than to potential confounding variables, such as environmental factors, changes in patient compliance, illicit substance use, or spontaneous fluctuations in symptom severity. Despite these limitations, the conclusion of Suzuki and colleagues that most patients do not benefit from the combination of conventional antipsychotics seems quite reasonable.

Polypharmacy with conventional agents probably represents a different set of clinical and theoretical questions than polypharmacy involving atypical agents, as is most commonly practised today. Unlike combinations involving atypical agents, polypharmacy with conventional agents was never widely practised in most countries and does not follow, to our knowledge, from any theoretical model. One exception is the combination of a low-potency, sedating agent at bedtime with a morning dose of a non-sedating higher potency agent. The utility of this approach, which aims at controlling side-effects rather than enhancing efficacy, was modestly supported by the data of Suzuki and colleagues. Antipsychotic agents, in theory, can be combined to achieve adequate additive D2 occupancy while reducing dose-dependent side-effects unique to each drug (such as sedation). This rationale may underlie the most common combination in current US clinical practice – the addition of an evening dose of quetiapine to daytime doses of less-sedating antipsychotics. While seemingly justified, this approach has run into considerable scepticism on the part of third-party payers who note the absence of any controlled data to support this relatively costly use of a sedating atypical agent rather than a generic benzodiazepine.

The current controversy in the United States over polypharmacy emerged following the introduction of atypical agents. Many factors may have contributed to the rapid rise of antipsychotic polypharmacy, from a relatively uncommon practice during the era of conventional neuroleptics to approx. 15–30% of patients today. First was the discovery that clozapine, the most effective antipsychotic agent, is a ‘dirty’ or highly non-selective drug – acting on a multitude of receptors directly or indirectly, including subtypes of dopaminergic, noradrenergic, serotonergic, histaminergic, norepinephrine, and serotonin receptors.
cholinergic and glutamatergic receptors. What Dr. Stahl has referred to as the ‘dirty little secret’ of antipsychotic polypharmacy (Stahl, 1999) may reflect in part the growing realization that optimal treatment of schizophrenia may be a ‘dirty’ business – we have largely lost hope that a single receptor will hold the key to this illness (Brunello et al., 1995; Goff and Coyle, 2001). Certainly, activity at D2 receptors is not solely responsible for clozapine’s markedly superior efficacy. Secondly, as clinicians adopted the approach of ‘cross-titration’ when switching from one atypical agent to the next, they discovered that some patients report the greatest relief of their symptoms during the ‘polypharmacy phase’ of the cross-titration compared to monotherapy with either agent. This observation may have resulted in some possibly beneficial polypharmacy. Unfortunately, many patients have ended up on combination regimens for the wrong reasons, such as premature interruption of a cross titration, or the unsystematic addition of a second (or third) agent ‘just to do something’, often during extremely brief hospital stays.

Is there any evidence supporting effectiveness for polypharmacy? The evidence is quite meagre (Freudenreich and Goff, 2002). The only published placebo-controlled, randomized, double-blind trial of polypharmacy was a 10-wk trial reported by Shiloh et al. (1997), in which the selective D2 antagonist, sulpiride, added to an optimal dose of clozapine, significantly improved outcomes in a sample of 28 schizophrenia patients. While encouraging, this one small positive study is hardly sufficient evidence to declare this approach substantiated.

Is there a rationale for polypharmacy? The conventional agents are believed to be equivalent in efficacy as a group and to share the same mechanism of action – D2 blockade. Unlike the standard practice for hypertension or seizures, in which agents of differing mechanisms are sequentially added until satisfactory efficacy is achieved, the conventional agents do not fit such a rationale for combination treatment and the findings of Suzuki and colleagues are consistent with this prediction of minimal benefit.

Certain atypical agents might better fit such a rationale for polypharmacy, but at present we have not sufficiently identified distinct mechanisms unique to individual drugs. Clozapine has most consistently demonstrated greater efficacy compared to conventional agents, but via largely unknown mechanisms. A recent meta-analysis (Davis et al., 2003) suggested that 5-HT2A antagonism, which has been identified as possibly contributing to certain advantages of atypical agents, did not differentiate the ‘second-generation’ agents that have established therapeutic superiority compared to conventional from those that have not. Amisulpride, which does not bind appreciably to 5-HT2A receptors, landed in the ‘more effective’ group along with clozapine, risperidone and olanzapine, whereas agents like quetiapine, ziprasidone and aripiprazole, that boast substantial 5-HT2A affinity did not achieve this status.

This leaves us with the unsettlingly vague conclusion that a small group of drugs may have therapeutic advantages mediated by uncertain mechanisms compared to conventional D2 blockers. This presumes that advantages are not merely the consequence of favourable dosing in comparison trials – a conclusion least controversial for clozapine (Davis et al., 2003). The positive study by Shiloh et al. (1997) supports the theory that clozapine possesses a primary therapeutic mechanism mediated by receptor activity other than its relatively weak D2 blockade. Increasing D2 occupancy by sulpiride is thought to have enhanced efficacy in some patients by amplifying this second mechanism of action. At least one uncontrolled trial has reported similar results with addition of the high-affinity D2 blocker, risperidone, to clozapine (Henderson and Goff, 1996).

It is possible that the efficacy of agents such as clozapine or quetiapine can be enhanced in some patients by occupying a greater number of D2 receptors with agents that are more ‘tightly bound’ to the D2 receptor, but certain atypical properties may be sacrificed (Kapur and Seeman, 2001). Preliminary results indicate that addition of risperidone, sulpiride and haloperidol to clozapine increases prolactin levels (Henderson et al., 2001; Kapur et al., 2001; Shiloh et al., 1997) and haloperidol, in theory, may cause extrapyramidal symptoms (Kapur et al., 2001). Obviously, larger controlled trials are needed to test the effectiveness and safety of this approach to polypharmacy. These studies should incorporate an important design element found in the study by Suzuki and colleagues – the increased antipsychotic dosage delivered in polypharmacy should be controlled. It must be clear that polypharmacy is not merely compensating for inadequate dosing of the monotherapy agent.

How should clinicians proceed in the absence of evidence or clear identification of mechanisms involved? As articulated by Suzuki and colleagues, adequate monotherapy trials should always be completed before contemplating polypharmacy. In the face of insufficient response, monotherapy trials should include clozapine whenever possible. Addition of a ‘tightly bound’ D2 antagonist, such as sulpiride, risperidone, or possibly aripiprazole, to clozapine may be an
appropriate next step if optimal treatment with clozapine is not effective. Clinicians need to monitor for emergence of side-effects, specify the duration of the trial (e.g. 6 wk), specify target symptoms, and document their assessment of benefit at the end of the trial. In the absence of clear improvement, combination treatment should be discontinued. Such a systematic approach may identify a small group of patients who benefit from combination treatment, whereas unsystematic polypharmacy clearly should be avoided.

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References


