ANTIPSYCHOTIC POLYPHARMACY OR MONOTHERAPY?*

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POLIFARMÁCIA VAGY MONOTERÁPIA?
A szindrómák és betegségek kezelése egyszerre több gyógyszerrel gyakori a pszichiátriában, éppen úgy, mint a belgyógyászatban. Annak ellenére, hogy a szakértők monoterápiát javasolnak, az antipszichotikus polifarmácia (APP) aránya egyre növekszik, különösen az atípusos antipszichotikumok bevezetése óta. A vonatkozó irodalom három kontrollált vizsgálatból és számos esetleírásból áll: ezekből az adatokból az APP hatásossága nem meggyőző. A legjobb eredményeket azok a vizsgálatok mutatták fel, ahol a clozapin hatást egy második antipszichotikummal potenciálták (augmentálták). A mellékhatások áttekintése azt mutatta, hogy az anticholinerg és extrapiramidális mellékhatások gyakoribbak APP mellett, mint monoterápiánál, azonban ezek a különbségek eltűnnek, mihelyt a dózist kiegyenlítik. Az APP kezelés költsége rendszerint meghaladja a monoterápia költségét, de túl kevés adat létezik erről.
A szakértők az APP-t a következő speciális esetekben javasolják: a) ha a pszichotikus beteg nem javult több gyógyszeres kezelés után, a clozapint beleértve; b) ha az átállás egyik antipszichotikumról egy másikra nem volt hatásos; c) típusos antipszichotikum atípusos mellé akut túlizgatott kórházi pszichotikusos betegeknek.
Az APP kivétel nélküli elítélése méltatlan: a tudatlan gyógyszerkezelés a tulajdonképpeni probléma. A pszichofarmakológia oktatásának továbbfejlesztése és a tudományos pszichofarmakológia előrehaladása fogja csak megvalósítani a specifikus antipszichotikus kezelést és az APP arányának csökkenését.
KULCSSZAVAK: polifarmácia, monoterápia, atípusos antipszichotikumok, típusos antipszichotikumok

SUMMARY
The concurrent use of more than one drug to treat syndromes and diseases is common in medicine as well as in psychiatry. Despite strong recommendation by experts to employ monotherapy whenever possible, the prevalence of antipsychotic polypharmacy (APP) has greatly increased, particularly since the advent of the Second Generation Antipsychotics (SGA). The literature which consists of three RCTs, several naturalistic cohort studies and numerous case reports does not show convincing evidence of APP efficacy. The best results were seen in studies of augmentation of clozapine response by a second antipsychotic. Studies which examined the side effect burden showed higher rates of anticholinergic and extrapyramidal side effects of APP compared to monotherapy, but these differences tended to disappear when total dosage was controlled for. The relative cost of APP may be higher than monotherapy, but very little data are available.
Experts recommend APP in a few special clinical situations: a) for augmentation when a patient fails to respond to adequate antipsychotic trials, especially with clozapine; b) in some instances of failed cross-taper of antipsychotics; c) adding a FGA to a SGA for agitation during acute treatment of psychosis.
Indiscriminate condemnation of APP is misdirected, the real culprit being incompetent pharmacotherapy. Improved education and advances in the science of psychopharmacology will lead to more specific antipsychotic therapies and ultimately to less need for APP.
KEYWORDS: polypharmacy, monotherapy, first generation antipsychotics, second generation antipsychotics

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Modern medicine has created an ever expanding list of effective therapeutic agents. As life expectancy increases and chronic diseases are better controlled, physicians are called upon to treat several coexisting conditions safely and effectively.

Polypharmacy implies the concurrent use of several drugs in the same patient. There are multiple definitions depending on types of medications, the prescribing situation or therapeutic value. A narrow definition of polypharmacy, for example might refer to a patient who is receiving several antihypertensives, while a wider definition may involve the treatment of several co-existing conditions such as chronic pain and depression with simultaneous antidepressants, sedative-hypnotics and analgesics. Classification may also be based on the relationship between the drugs used concurrently:

a) Same-class polypharmacy – more than one compound from the same class to provide additive effects (e.g. two phenothiazines).

b) Multi-class polypharmacy – full therapeutic doses from different classes (e.g. lithium plus antipsychotic) to enhance therapeutic effect.

c) Augmentation – adding a second medication in lower dose to a first drug at full therapeutic dose for enhanced effect.

d) Adjunctive polypharmacy – use of a second medication to counteract side effects of the first drug while adding to its therapeutic effects (e.g. adding a small dose of a sedative/anticholinergic antipsychotic to a non-sedating D2-blocker).

Terminology tends to carry weight in psychiatry as it does in other branches of medicine.

"Polypharmacy" has been a pejorative term, tolerated at best and taboo at worst, while phrases such as "combination therapy" or "co-prescribing" have been looked on more favorably.

This paper focuses on the use of two or more antipsychotics. The term "Antipsychotic Polypharmacy" (APP) was chosen despite the negative connotations as it is still the most frequently employed term in the literature.

EPIDEMIOLOGY

There has been an upsurge of interest in polypharmacy in the field of psychiatry as reflected by a recent front-page article in the Wall Street Journal (2004) as well as an entire book (Ghaemi 2002) devoted to this subject. The renewed interest is more than likely related to the marked increase in the use of polypharmacy and to the new emphasis on evidence-based clinical decision-making. My colleagues and I reviewed APP 25 years ago (Gardos et al. 1980) which at that time mostly consisted of prescribing more than one phenothiazines or adding reserpine. The practice of APP was roundly condemned (Ayd 1973) as being irrational, dangerous, unscientific, and a cover-up for diagnostic uncertainty and ignorance. Nonetheless, high rates of polypharmacy were observed in public mental hospitals in North America as well as in Europe (Gardos et al, 1980). The introduction of the Second-Generation Antipsychotics (SGA) has radically altered the pharmacotherapy of psychotic disorders by virtue of their efficacy for negative symptoms and lesser potential for inducing EPS. Because each SGA exerts important and unique pharmacological actions beyond D2 receptor antagonism each drug may be thought of as representing a type of poly-

Table 1. Increasing Prevalence of APP

Authors	Population	Change in APP prevalence	Comment
Centorrino et al. 2002	Hospitalized psychotic and affective patients	1993: N=299; 5.7% 1998: N=399; 20%	Mean doses of APP higher than monotherapy dosage (371 vs. 317 CPZE)
McCue et al. 2003	Chart review of discharged schizophrenics	1995: N=459; 0% 2000: N=584; 15.9%	Olanzapine + haloperidol was the most frequent combination
Clark et al. 2002	Pharmacy records of schizophrenic and schizo-affective patients	N=800 1995: 5.7% 1999: 24.3%	
Grohman et al. 2004	9 German and 1 Swiss Hospitals	1995: N=715; 24.3% 2001:N=980; 31.5%	
Ganguly et al. 2004	Schizophrenics in Medicaid Database (Georgia and California)	N=32.280 1998: 32% 2000: 41%	Quetiapine showed high positive association with APP

pharmacy thereby blurring the distinction between FGA and SGA. Because of the complex profile of SGA compounds it is almost impossible to predict the clinical effects of combining two or more SGA on a scientific basis. Data comparing different combinations of FGA and SGA with monotherapy are largely empirical.

There is convincing evidence to show that APP has increased markedly since SGA became available. A recent review by Stahl and Grady (2004) documents the frequent use of APP in contemporary pharmacotherapy: 5-18% of outpatients and up to 50% of inpatients are treated with APP. They conclude that despite success in individual patients there is no compelling evidence to support long-term APP. Other objections to APP involving SGA include greatly increased cost, increased side effects and the potential for negative drug interactions. At the same time Stahl and Grady (2004) acknowledge that high doses of SGA likewise show little additional efficacy, may double the cost and may increase side effects.

EFFICACY AND EFFECTIVENESS OF APP

The dearth of well-designed studies of APP is hardly surprising. Neither Industry nor clinical science is likely to give high priority to studying APP. Effectiveness is mostly derived from uncontrolled cohort studies and retrospective chart reviews. Only three randomized controlled trials of APP were found in the literature each involving clozapine. Shiloh et al (1997) added sulpiride (or placebo) to 28 schizophrenics partially responding to clozapine. Mean BPRS total scores decreased by 8.7 on the combination vs. 2.3 on clozapine + placebo. Half the patients, however, showed no improvement on the combination. The second RCT compared clozapine, chlorpromazine, and their combination in 57 schizophrenic inpatients. Clozapine monotherapy and the combination were superior to chlorpromazine monotherapy on the BPRS (Rother et al. 1989). In a recently completed RCT risperidone or placebo were added to clozapine in 30 schizophrenics partially responsive to clozapine (Yagcioglu et al. 2004). There was significantly greater improvement in the clozapine–placebo group compared to the clozapine–risperidone group on the PANSS Positive Symptom subscale, as well as on two measures of Executive Function. The addition of risperidone (x= 5.1 mg/d) may have diminished rather than enhanced the effects of clozapine (x=516 mg/d), possibly due to high dosage causingexcessive DA blockade.

Centorrino et al. (2004) published a retrospective case-control study of multiple versus single antipsychotic treatment in 70 pairs of psychotic inpatients. While clinical improvement scores were similar, the APP group yielded higher median antipsychotic doses , 55% longer hospital stays and 56% more side effects. These differences need to be interpreted with caution, since the APP group may have included less treatment-responsive patients.

The bulk of the published data on combining antipsychotics features clozapine. Uncontrolled clinical trials on augmentation of clozapine with various FGA or SGA tend to show favorable results. Co-administration of amisulpride, a selective D2 and D3 receptor blocker, and clozapine in refractory schizophrenics led to substantial improvement in positive and negative symptoms in two separate trials (Munro et al. 2004; Agelink et al. 2004). Positive results were also when loxapine, risperidone, pimozide, olanzapine (Yuzda 2000) or ziprasidone (Stahl and Grady 2004) were used to augment clozapine.

Combinations of other SGA with FGA led to inconsistent results. Waring (1999) found that about 2/3 of 31 patients improved or were discharged from the hospital as a result of SGA-FGA combination therapy. Taylor et al. (2002), however, reported little benefit from SGA–FGA combinations.

Quetiapine, a weak D2 blocker was found to be the SGA most often combined with FGA (Centorrino 2004, Stahl et al. 2004; Freudenreich and Goff; Yuzda, Grohman 2004) probably because of the need to augment D2 receptor blockade.

Two studies attempted conversion of APP to monotherapy. In Godleski et al.'s report (1989) 8 of 14 patients showed marked psychotic decompensation when converted to a single antipsychotic drug. Suzuki et al. (2004), however, were mostly successful in converting 44 schizophrenics to monotherapy: 24 remained stable, 10 improved and 10 became clinically worse.

In summary, the sparse research data reveals little or no superiority of APP over monotherapy. The case reports and cohort studies point to effectiveness of APP in some treatment refractory psychotic patients, particularly when clozapine was augmented by another antipsychotic.

SIDE EFFECTS OF APP

A few studies have provided side effect data of APP compared to monotherapy. In general, more side effects were seen with APP than with single antipsychotics. Procyshyn et al. (2001) found significantly greater use of anticholinergic agents in schizophrenic patients discharged on APP than those discharged on monotherapy. Although SGA are associated with rare EPS, with APP the potential for EPS is increased since using high doses or adding an FGA or SGA could lead to loss of atypicality (Freudenreich, Goff 2002). Centorrino et al. (2004) did in fact report more EPS in APP patients than in monotherapy controls, but higher doses and greater use of haloperidol in the APP group may have accounted for the difference.

Both FGA and SGA cause an up-regulation of dopamine D2 receptors and have been associated with tardive dyskinesia (TD) development. While isolated cases have been reported for every SGA, the incidence of TD is much higher in FGA both in adults and in the elderly (Correll et al. 2004).

Dosage is an important variable: Correll et al. (2004) suggested that higher doses of risperidone led to higher rates of EPS and conceivably to higher rates of TD as well and such a relationship between antipsychotic dose and risk for EPS and TD might be true for other SGA as well. Studies specifically addressing TD risk from APP have not been found. Extrapolating from the data on single antipsychotics it may be surmised that APP involving FGA would carry higher risk of TD than APP only involving SGA, and that the total neuroy be positively correlated with TD development.

The use of SGA has been associated with increased risk for the metabolic syndrome: weight gain, Type II Diabetes Mellitus, and dyslipidemia. (ADA et al. 2004) There are clear differences among SGA in their propensity to cause metabolic abnormalities and these differences need to be borne in mind when APP is employed. For instance, Reinstein et al. (1999) switched a group of 65 clozapine-treated patients who gained an average of 6.5 kg after 6 months to a combination of quetiapine and clozapine in equal doses. After 10 months on the combination, patients lost an average of 4.2 kg and their glycemic control improved. This study illustrates that APP does not necessarily carry higher risk of the metabolic syndrome than monotherapy.

Among other reported adverse effects of APP reduced survival has been suggested (Waddington et al. 1998) but this relationship awaits confirmation.

COST

Despite claims that APP inflates the cost of antipsychotic drug therapy convincing data are hard to come by. Common sense would suggest that APP is more costly than monotherapy because more pills are involved. While this is true more often than not, there are numerous exceptions, and it is theoretically possible for APP to be cheaper than monotherapy, when a more expensive antipsychotic drug is combined with a cheaper one which inhibits the metabolism of the former. In the one relevant study published, Stahl et al (2004) found higher cost of APP compared to monotherapy but the differences were confounded by differences in efficacy between the two SGA studied.

CONCLUSIONS

The relevant literature reviewed above failed to show superior efficacy for APP over monotherapy. There was a tendency for APP to cause more adverse effects than monotherapy but the differences were either minor or confounded by dose differences.The lack of well-controlled clinical trials argues against drawing sweeping generalizations from the data. There were circumstances identified, however, where APP may merit consideration. Canales et al (1999) cited the following specific indications for APP:

1. Suboptimal clinical response after adequate monotherapy trials with several SGA including clozapine. Numerous publications showed efficacy of adding a second antipsychotic drug, whether SFA or FGA . There are several practical disadvantages of clozapine therapy, such as heavy side effect burden, need for regular blood tests, and high cost which detract from the drug's clinical utility. (Wilf 2004)

2. During transition from one antipsychotic to another. Switching antipsychotics occurs frequently in clinical practice, and gradual cross-taper is the recommended technique. If clinical deterioration takes place after the first antipsychotic is withdrawn, it may be reinstated and the combination kept if the patient recompensates. A specific example from the author's practice : a patient on quetiapine 600 mg HS relapsed and was hospitalized. She was treated with aripiprazole 30 mg/d and discharged much improved. At the follow-up visit she was psychiatrically stable except for marked insomnia. Adding quetiapine

200 mg HS relieved her insomnia. The addition of an HS dose of quetiapine to a less sedating antipsychotic is in fact the most commonly employed APP in current practice in the US (Freudenreich and Goff 2004).

3. In acutely psychotic patients who exhibit significant agitation or aggression, but the use of APP in these situations is usually only temporary: as patients recompensate the second antipsychotic is withdrawn and continued monotherapy is the rule.

How is one to reconcile these recommendations for using APP with the admonition by most experts against using APP? Leo Hollister, one of the pioneers of psychopharmacology put it succinctly 30 years ago: "Polypharmacy is not particularly good but may sometimes be necessary" (Hollister 1975). Instead of polypharmacy vs. monotherapy the real issue may be expert vs. incompetent pharmacotherapy, whether dealing with APP or monotherapy. Improper APP can be ineffective, costly and toxic just as much as inappropriate monotherapy. New research will pave the way towards more specific and more effective pharmacotherapy and will eventually obviate the need for APP.

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