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Adjunctive Medication in the Maintenance Treatment of Schizophrenia and its Conceptual Implications

SAMUEL G. SIRIS

Beyond the continuing use of neuroleptic medication, psychopharmacological treatment approaches during the maintenance phase of schizophrenia often involve adjunctive medication. Appropriate use of such 'polypharmacy' can be crucial to patients in achieving their optimal levels of symptom management and functional capacity, although the risks of side-effects and medication interactions must be weighed. This paper reviews the use of adjunctive anti-Parkinsonian medication, benzodiazepines, propranolol, antidepressants, lithium, and carbamazepine in this context. It also explores a strategy of identifying secondary syndromes in the longitudinal course of schizophrenia which can be approached psychopharmacologically.

Neuroleptic medication has represented the core of the psychopharmacological treatment of schizophrenia for decades, and it is now well established that maintenance neuroleptic treatment in some form is required to avert an unacceptably high rate of relapse into psychosis (Davis, 1975; Kane, 1990). Nevertheless, these patients are not 'cured', and in a large number of cases serious functional impairment and subjective distress remain, even though the limiting factor may no longer be the patients' level of psychosis (Group for the Advancement of Psychiatry (GAP), 1992). This continuing morbidity invites further medication interventions in an effort to relieve suffering and enhance performance. These adjunctive pharmacological strategies, and their implications in the context of the longitudinal course of schizophrenia, are reviewed in this paper.

A number of problems which schizophrenic patients encounter have been attributed to side-effects of neuroleptic medication itself. This is doubtless often the case, and has led to variations in neuroleptic maintenance strategies, including lower dosages (Goldstein *et al*, 1978; Kane *et al*, 1983; Hogarty *et al*, 1986; Marder *et al*, 1987; Kane, 1990) or intermittent treatment (Carpenter *et al*, 1982; Herz *et al*, 1982, 1991; Kane, 1990). Such approaches may indeed lead to lower incidences of extrapyramidal side-effects, reduced rates of tardive dyskinesia, and improved patterns of psychosocial adjustment. Nevertheless, other adverse symptoms during the longitudinal course of schizophrenia seem not to be associated with neuroleptic medication, and, crucially, there also exists a substantial set of symptoms and states about which it can be quite unclear whether or not the use of neuroleptic medication plays a role, either as a primary cause or as an exacerbating factor.

Such a circumstance should not be unexpected, of course, because the currently most widely accepted hypothesis concerning the pathophysiology of schizophrenia is that it represents a disorder of systems involving dopaminergic neurotransmission (Meltzer, 1985; Carlsson, 1988; Reynolds, 1989; Davis *et al*, 1991), and the mode of action of neuroleptic medication is dopaminergic receptor blockade. As a result of this potential heuristic blurring, and because maintenance-phase patients with schizophrenia would be expected to be undergoing treatment with neuroleptic medication in any event, this review empirically considers the use of all types of adjunctive medication, independent of whether they have been primarily conceptualised as treatment for neuroleptic side-effects or whether they have been traditionally thought of as treatment for symptom clusters distinct from the realm of neuroleptic activity. It then proposes a strategy for exploring secondary syndromes in the longitudinal course of schizophrenia as a basis for formulating plans for adjunctive psychopharmacological intervention and for potentially expanding our understanding of the heterogeneity of this complex disorder.

Adjunctive anti-Parkinsonian medication

The addition of anti-Parkinsonian medication to neuroleptic regimens is generally recognised to be useful during acute treatment to reduce the incidence and severity of dystonic reactions as well as Parkinsonian stiffness and tremor (Gelenberg, 1987; Arana *et al*, 1988; Lavin & Rifkin, 1991*a*). More controversial is the requirement for anti-Parkinsonian medication over the course of extended maintenance treatment with neuroleptic agents (Rifkin *et al*, 1978; Baker *et al*, 1983; Lake *et al*, 1986; Gelenberg, 1987;

Barnes, 1990; World Health Organization, 1990; Lavin & Rifkin, 1991*b*). This controversy is fuelled by the fact that anti-Parkinsonian agents may themselves have side-effects, and also by the fact that at least some of the anti-Parkinsonian agents are thought to have the potential to be abusable.

Many differences of opinion concerning maintenance anti-Parkinsonian treatment also stem from the serious methodological weaknesses of the studies which have been done to date regarding this subject (Lavin & Rifkin, 1991*b*). Many of the published studies of discontinuation of maintenance anti-Parkinsonian medication have lasted only a few weeks, and none of the double-blind studies continued for more than three months. The results are based, at best, on the ratings of one or another extrapyramidal-system side-effect rating measure and/or whether a treating clinician elected to restart anti-Parkinsonian medication. In studies which attempted specifically to include measures of akinesia and akathisia in the assessment of extrapyramidal side-effects, incidences as high as 94–98% of these reactions were found (Chien *et al*, 1974; Manos *et al*, 1981*a*,*b*), but most of the studies which have been reported did not examine subjects for these particular manifestations and found lower rates of extrapyramidal side-effects.

Additionally, other pivotal outcome measures, such as social and vocational performance, neuroleptic compliance, and rates of hospital readmission with and without adjunctive anti-Parkinsonian medication have not been explored, nor has there been a direct study comparison of the utility of adjunctive anti-Parkinsonian treatment with a neuroleptic dose-reduction strategy. Indeed, it has been posited that anticholinergic anti-Parkinsonian medication may reduce plasma neuroleptic levels (Loga *et al*, 1975), thus constituting a *de facto* neuroleptic-reduction trial. However, more recent data appear to contradict that suggestion (Simpson *et al*, 1980; Hitri *et al*, 1987). From a pathophysiological perspective, one group has further suggested, based on limited data, that anticholinergic medication may directly counteract cholinergic processes postulated to be involved in the specifically negative symptoms of schizophrenia, while simultaneously potentially exacerbating positive symptoms by related mechanisms involved in a biochemical 'balance' hypothesis (Tandon & Greden, 1989). This is a hypothesis which merits further investigation, especially in terms of whether the positive symptoms involved would in fact become clinically manifest or significant in patients who were otherwise relatively stable and receiving maintenance treatment with concomitant neuroleptic medication.

Side-effects of anti-Parkinsonian agents

The most frequently employed anti-Parkinsonian agents are anticholinergic compounds such as benztropine, trihexyphenidyl, procyclidine, and biperiden. Familiar side-effects of these drugs include dry mouth, blurred vision, and constipation. These side-effects are not generally medically dangerous, and are chiefly notable in terms of their annoyance value, although dry mouth can contribute to dental caries and blurry vision can be dangerous in such situations as driving. Often complaints secondary to anticholinergic side-effects diminish over time, although it is not entirely clear whether the patients compensate in some fashion or merely tire of complaining. The anticholinergic activity of anti-Parkinsonian compounds, however, can be more serious in the elderly or medically compromised patient. Obstipation can be medically severe, narrow-angle glaucoma can be seriously aggravated, and patients with prostatic enlargement may develop urinary obstruction. Heart rate and cardiac conduction can also be adversely influenced by anticholinergic compounds in cardiac patients.

Anticholinergic anti-Parkinsonian agents may also be associated with memory deficits as a side-effect (Potamianos & Kellet, 1982; Baker *et al*, 1983; Calev, 1983; Gelenberg *et al*, 1989). In terms of specific testing, however, this deficit is most likely to appear as an impairment in recent or 'free recall' verbal memory tasks, but less likely to impair other memory functions (Tune *et al*, 1982; Perlick *et al*, 1986; McEvoy, 1987; McEvoy & Freter, 1989; Spohn & Strauss, 1989; Strauss *et al*, 1990). Anticholinergic drugs may also affect the perception of the passage of time and the subjective sense of ability to remember (Gelenberg *et al*, 1989). Most young, physically healthy patients do not experience memory decrements which are prominently detectable subjectively or meaningful from a functional perspective. However, a smaller number of patients, perhaps particularly those with enlarged ventricles (Fayen *et al*, 1988), do experience notable memory problems. In those individuals it is a side-effect worth avoiding if possible, since a memory decrement may take a further toll in terms of a schizophrenic patient's functional reserve, which he or she can ill afford in the struggle to re-establish social and vocational competencies. Furthermore, dissatisfactions concerning this side-effect, like others, can unfortunately predispose ultimately to general medication non-compliance.

Additionally, the emergence of symptoms of tardive dyskinesia has been associated with the use of anticholinergic anti-Parkinsonian medication

(Bergen *et al*, 1992). This effect needs to be distinguished from the aetiology of tardive dyskinesia, however. Anticholinergic anti-Parkinsonian drugs may not actually contribute to the aetiology of tardive dyskinesia. Rather, they may merely make its symptomatology more prevalent (i.e. 'unmask' it) in a way which is reversible with the discontinuation of the anti-Parkinsonian agent (Chouinard *et al*, 1988; Gerlach & Casey, 1988). Alternatively, anti-Parkinsonian drug use may simply represent a surrogate marker for neuroleptic-induced Parkinsonism, which itself has been found to be associated with vulnerability to tardive dyskinesia (Chouinard *et al*, 1988; Kane *et al*, 1988).

Finally, anticholinergic anti-Parkinsonian agents have been reported to have a potential for abuse and this has led to warnings of caution in their use (Crawshaw & Mullen,1984; Pullen *et al*, 1984; Dilsaver, 1988; Wells *et al*, 1989). Generally, however this issue has been noted in single and multiple case reports, so that its true prevalence remains unclear. One of the fundamental clinical problems associated with the issue of anti-Parkinsonian abuse is the difficulty which may exist in distinguishing patients who are truly abusing one of these substances from patients who insist on receiving one of these agents because it legitimately helps them to 'feel more normal'. In this latter case, which may occur frequently, such use, even when unauthorised, hardly represents true 'abuse'.

One approach to the avoidance of the side-effects of the anticholinergic anti-Parkinsonian agents is through the use of amantadine (Hitri *et al*, 1987; Fayen *et al*, 1988; Gelenberg *et al*, 1989). Amantadine is an agent which is thought to stimulate directly those nigrostriatal dopamine receptors which affect movement abnormalities, without being an agonist for those mesolimbic dopamine receptors which are considered to be responsible for symptoms of psychosis (Bailey & Stone, 1975; Allen, 1983). As a result, anti-Parkinsonian benefits can be attained without anticholinergic side-effects. In rare cases, though, psychosis may nevertheless be exacerbated by amantadine (Nestelbaum *et al*, 1986). On the other hand, it is worth noting that benztropine, which is usually categorised as an anticholinergic anti-Parkinsonian agent, has potent dopamine-agonist properties as well (Modell *et al*, 1989).

The issue of akinesia and akathisia during long-term treatment

All the above potential adverse consequences of long-term anti-Parkinsonian medication treatment require careful consideration in relationship to the potential for substantial benefit which can be derived from the long-term use of these compounds. This benefit is obvious when Parkinsonian rigidity, tremor, or reduction of gross accessory motor movements is prominent and cannot be managed by neuroleptic dosage reduction. The benefit is similarly important, however, when more subtle, but no less debilitating, symptoms of akinesia require treatment with maintenance anti-Parkinsonian medication. This more subtle form of akinesia may involve a reduction in normal spontaneity, so that the affected individual loses his or her ability to initiate or sustain behaviour in a natural fashion (Rifkin *et al*, 1975, 1978; Van Putten & May, 1978; Siris, 1987; Van Putten & Marder, 1987). Its rate of occurrence is substantial, being noted in between 27% and 47% of neuroleptic-treated patients (Rifkin *et al*, 1978; Van Putten & May 1978; Van Putten & Marder, 1987). Such individuals suffer major psychosocial impairment as they present their passive 'bump-on-a-log' appearance to the world, an appearance which is in fact determined on an extrapyramidal rather than a psychological basis. Another form of akinesia, which can also be devastating socially, is extrapyramidal stiffness which affects the small muscles of the face and/or larynx. This form of akinesia results in the patient presenting a rather fixed vacuous-looking expression and/or a monotonous voice.

Either one of these forms of akinesia can occur in the absence of more easily appreciated stiffness in large muscle groups or obvious reduction in accessory motor movements. Indeed, akinesia in 'pure culture' has been noted to occur approximately twice as often as it occurs in conjunction with prominent signs of large-muscle rigidity (Van Putten & May, 1978; Rifkin *et al*, 1978). Each of these forms of akinesia may also be accompanied by secondary anhedonia, and can easily be mistaken for either 'negative symptoms' or depression. Therefore, it is an appropriate strategy to administer a test trial of a full dose of anti-Parkinsonian medication to any neuroleptic-maintained schizophrenic patient who appears to have the syndrome of negative symptoms or secondary depression, because some such patients can benefit substantially from ongoing adjunctive anti-Parkinsonian medication treatment (Carpenter *et al*, 1985; Siris, 1991; Bermanzohn & Siris, 1992). A full test dose of anti-Parkinsonian medication is ordinarily considered to be 6 mg/day of benztropine, or its equivalent, in divided doses because of its short (approximately eight hours) half-life. What constitutes a particular individual's full test dose, however, may deviate considerably, since a tenfold variability in benztropine metabolism has been reported (Tune & Coyle, 1980). The emergence of anticholinergic

side-effects may therefore be a valuable biological marker for the adequacy of an anticholinergic anti-Parkinsonian drug trial in treating possible akinesia.

Another important and potentially debilitating extrapyramidal side-effect, which can occur in either a blatant or subtle form, and which can at times be treated with anti-Parkinsonian medication, is the motor-restlessness syndrome of akathisia (Van Putten, 1975; Siris, 1985; Barnes, 1989; Sachdev & Lonergan, 1991). Its rate of occurrence has been reported to be between 14% and 75% in various studies, depending on patterns of neuroleptic dosage and the method of assessing akathisia, and it probably occurs, at least to some degree, as a persistent phenomenon during neuroleptic treatment in approximately 40% of cases (Sachdev & Lonergan, 1991). As is the case with akinesia, akathisia is easy to recognise in its blatant form but equally easy to misconstrue when its presentation is subtle. In the latter case, its stigmata may be overtalkativeness, wandering into 'other people's space', and/or a generalised predisposition to behaviour in situations where patience or reflection might be more adaptive (Siris, 1985). Unfortunately, the syndrome of akathisia is less likely to be responsive to anti-Parkinsonian agents than the syndrome of akinesia, but if it is responsive to these drugs in a specific individual it certainly warrants their use (Fleischhacker *et al*, 1990; Sachdev & Lonergan, 1991). If neuroleptic-induced akathisia is not responsive to anti-Parkinsonian agents, it may nevertheless be responsive to adjunctive propranolol or benzodiazepines (see below), or possibly other agents, such as clonidine or amantadine (Fleischhacker *et al*, 1990; Sachdev & Lonergan, 1991), which could then also be continued as needed over the longer-term maintenance course.

Adjunctive benzodiazepines

Historically, polypharmacy with adjunctive benzodiazepines has been recommended relatively infrequently in the treatment of schizophrenia, despite suggestions of its potential utility and the relatively wide therapeutic index of benzodiazepines (Christison *et al*, 1991; Wolkowitz & Pickar, 1991). More recently, though, it has become acknowledged that benzodiazepines can be a valuable adjunct to neuroleptics in the treatment of acute psychosis, allowing not only more rapid control of symptoms but also the usage of lower neuroleptic doses in a number of situations (Arana *et al*, 1986; Dubin *et al*, 1986; Salzman *et al*, 1986; Douyon *et al*, 1989; Garza-Trevino *et al*, 1989; Bodkin, 1990; Barbee *et al*, 1992; GAP, 1992). It may be that this will prove to be the case as well with maintenance treatment, with the obvious benefits to be derived from lowered neuroleptic maintenance doses, but this has not yet been properly tested or established. While response rates to adjunctive benzodiazepines approached 50% in a meta-analysis of controlled studies (most of which, however, involved acutely psychotic patients or brief – six weeks or less – treatment trials in chronic or maintenance-phase patients), the available reports suggest wide individual variability in terms of patient response and are inconsistent on the issue of how well the benefits of adjunctive benzodiazepines are maintained over time (Wolkowitz & Pickar, 1991). While at least some patients who initially do well appear to continue to benefit for as long as they are followed (in excess of a year) (Wolkowitz *et al*, 1992), controlled studies are approximately evenly divided on the question of the utility of an adjunctive benzodiazepine in chronic schizophrenic populations, leaving the impression that a small subgroup of chronic schizophrenic patients benefit from the addition of adjunctive benzodiazepine compared with placebo (Christison *et al*, 1991).

Although reports available to substantiate the thesis are limited, because many studies have not selected or stratified for anxiety, it is possible that benzodiazepines may be specifically useful as adjunctive medication in the treatment of schizophrenic patients with prominent symptoms of anxiety (Kellner *et al*, 1975; Donaldson *et al*, 1983; Csernansky *et al*, 1984; Wolkowitz *et al*, 1988; Pato *et al*, 1989; Christison *et al*, 1991; Wolkowitz & Pickar, 1991), post-traumatic stress (McGorry *et al*, 1991), or panic (Sandberg & Siris, 1987; Kahn *et al*, 1988; Cutler & Siris, 1991). In particular, the elegant cross-over study by Kellner *et al* (1975), in which three of six patients selected for anxiety responded favourably in multiple double-blind cross-overs between chlordiazepoxide and placebo would appear to support this hypothesis. If such is the case, it would be consistent with the notion that recognisable secondary clinical syndromes, such as those of anxiety in schizophrenia, represent specifically treatable entities. Furthermore, ongoing psychotic symptoms such as hallucinations and delusions, as well as less-specific symptoms such as tension, hostility, excitement, and social withdrawal, may be diminished when some schizophrenic patients are treated with adjunctive benzodiazepines (Donaldson *et al*, 1983; Wolkowitz *et al*, 1988; Christison *et al*, 1991; Wolkowitz & Pickar, 1991), and it is also possible that 'depressive symptoms' may be reduced in some cases (Pato *et al*, 1989; Wolkowitz & Pickar, 1991).

Recent research has often focused on the question of whether benzodiazepines might be useful adjuncts

in the treatment of schizophrenic patients who manifest specifically 'negative' symptoms (Csernansky *et al*, 1984, 1988; Wolkowitz *et al*, 1988; Wolkowitz & Pickar, 1991). However, the results of these reports are somewhat contradictory. Moreover, they are weakened by the fact that the studies in question did not vigorously attempt to rule out the potential confound of neuroleptic-induced akinesia among those patients identified as having negative symptoms, and did not systematically attempt either to include, exclude, or stratify for, those patients who might be manifesting concomitant symptoms or syndromes of anxiety. This may be an important issue in the context of at least some 'negative symptom' patients having been noted to have higher levels of anxiety (Siris *et al*, 1988; Stampfer, 1990). Since it is possible that at least a proportion of schizophrenic patients with phenotypic 'negative' symptoms may benefit from the addition of a benzodiazepine to their neuroleptic regimen, a therapeutic trial of an adjunctive benzodiazepine may be clinically warranted in patients who have negative symptoms which are otherwise unresponsive.

Additionally, benzodiazepines may be useful adjuncts in the treatment of neuroleptic-induced akathisia (Kutcher *et al*, 1989; Fleischhacker *et al*, 1990; Sachdev & Lonergan, 1991). The restlessness of akathisia, of course, could be difficult, if not impossible in some cases, to differentiate from anxiety, or from the agitation which may accompany subjective anxiety. Nevertheless, the anti-akathisia effect of benzodiazepines also appears to be a clinically replicable finding. Therefore long-term use of an adjunctive benzodiazepine could be justifiable as well in cases of akathisia which are unresponsive to lowering of the neuroleptic dose, or where the neuroleptic dose cannot be lowered without other deleterious effects.

Of course, acute, and especially long-term, use of benzodiazepines needs to be considered in the light of the potential side-effects of these agents. Benzodiazepines may be somewhat sedating (this effect may diminish over time), ataxia-inducing, habit-forming or possibly disinhibiting or psychotogenic (Karson *et al*, 1982; Arana *et al*, 1986; Wolkowitz *et al*, 1988; Dixon *et al*, 1989; Wolkowitz & Pickar, 1991). Psychotic rebound following benzodiazepine withdrawal may also be a risk (Karson *et al*, 1982; Roberts & Vass, 1986; Wolkowitz *et al*, 1988). Obviously, therefore, the dosages of benzodiazepines employed should be the minimum ones necessary to achieve the desired effects – as, of course, is the case for the neuroleptics as well.

Adjunctive propranolol

The l-isomer of propranolol may also be a valuable adjunct in the treatment of neuroleptic-induced akathisia (Adler *et al*, 1986, 1987*a*; Kramer *et al*, 1988; Fleischhacker *et al*, 1990; Adler *et al*, 1991), probably through the mechanism of β_1-adrenoreceptor blockade (Dumon *et al*, 1992). One study has suggested that this effect may be more pronounced when the propranolol is used in conjunction with an anticholinergic anti-Parkinsonian agent (Irwin *et al*, 1988), but propranolol is apparently often beneficial even without other adjunctive anti-Parkinsonian agents, or in patients whose akathisia may have been unresponsive to anticholinergic drugs or benzodiazepines. Interestingly, the usefulness of propranolol in the treatment of the agitation of akathisia appears to be independent of any specifically anxiolytic effect (Adler *et al*, 1986), although, here again, distinguishing clinically between the restlessness of akathisia and the restlessness of anxiety in schizophrenic patients may be difficult.

Propranolol may also be a useful adjunct to neuroleptic agents, separate from the issue of akathisia, in terms of enhancing or augmenting antipsychotic action in patients otherwise considered to be refractory or hyporesponsive, although this issue remains controversial (Donaldson *et al*, 1983; Ananth & Lin, 1986; Berlant, 1987; Lader, 1988; Lipinski *et al*, 1988; Christison *et al*, 1991). In this case, as in the case of treatment of akathisia, the strategy of propranolol dosing may be important in the avoidance of autonomic and toxic side-effects (Ananth & Lin, 1986). Indeed, it has been reported that propranolol can be used with general safety in substantial dosages in the neuroleptic-refractory population, but that adverse effects are best avoided by not raising the dose too rapidly. Raising the dose by as much as 40 mg/day in divided doses appears to be safe for patients with akathisia, and favourable effects in terms of this symptom are often rapidly achieved at dosages maintained at about 120 mg/day. It is unlikely that patients with akathisia will respond at higher doses if they have not responded at 120 mg/day (Fleischhacker *et al*, 1990). However, much higher doses may be both safe and useful in certain patients with schizophrenia, and should not be avoided if they are required in carefully selected cases.

Adjunctive antidepressants

It has become generally recognised that a substantial proportion of schizophrenic individuals suffer from a phenotypic syndrome of secondary depression

during intervals in the longitudinal course of their disorder, during which they are not flagrantly psychotic (McGlashan & Carpenter, 1976; House *et al*, 1987; Bartels & Drake, 1988; Johnson, 1988; Leff *et al*, 1988; Barnes *et al*, 1989; Hirsch *et al*, 1989; Siris, 1991). The most frequent estimate is that this occurs in 25% of individuals; however, estimates vary widely depending on the definition of 'depression' and the interval under consideration (Siris, 1991). While the biological meaning of this descriptive phenomenon is not well understood, empirical studies have often, but not always, indicated that the gradual addition of adjunctive tricyclic antidepressants to ongoing neuroleptic regimens is frequently of substantial clinical value (see Siris (1991) for review). Full-dose and full-duration antidepressant trials, comparable with trials for the treatment of primary depression, appear to be required. For example, in the only published study to utilise the ICD–10 diagnostic criteria for post-psychotic depression, and one which also made a stringent attempt to rule out patients with akinesia, 42% of patients receiving adjunctive imipramine (gradually increased to 200 mg/day) were rated as much or very much improved, as compared with only 12% of a cohort receiving adjunctive placebo (Siris *et al*, 1987).

Caveats in adjunctive-antidepressant work include the necessity for a careful trial of adjunctive anti-Parkinsonian medication to attempt to rule out the potentially confounding syndrome of neuroleptic-induced akinesia (Siris, 1987), and the difficulty in distinguishing the syndrome of depression in this population from transient disappointment or more-enduring demoralisation reactions. Another caution in the use of antidepressants in schizophrenia has been the concern that they might predispose to a re-exacerbation of psychosis, since antidepressant addition seems to retard the resolution of psychosis in schizophrenic patients acutely admitted to hospital (Kramer *et al*, 1989). However, such exacerbations appear to occur relatively rarely and mildly in otherwise generally stable schizophrenic patients who are not flagrantly psychotic, and who are maintained on neuroleptic medication (Siris, 1991). Furthermore, if and when an exacerbation of psychosis does occur under these conditions, it is generally well controlled with an increment in the neuroleptic dosage (Prusoff *et al*, 1979; Siris *et al*, 1987; Siris, 1991). An additional caution involves the fact that tricyclic antidepressants and neuroleptic agents compete for the same hepatic P-450 metabolic pathway, so that when one is in use the concomitant use of the other may result in an increase in plasma level of the first (Kragh-Sorenson *et al*, 1977; Nelson & Jatlow, 1980; Siris *et al*, 1982). Finally, of course, all the usual side-effects of antidepressant medication, such as orthostatic hypotension, peripheral anticholinergic effects, and exacerbation of cardiac conduction defects, need to be considered.

Little work has been conducted into the question of maintenance adjunctive-antidepressant treatment for patients with secondary depression in schizophrenia. The one double-blind study which has been performed involving this issue, however, does suggest that treatment of indefinite duration may be beneficial to those patients who have a favourable response initially (Siris *et al*, 1989*b*; Siris *et al*, 1993).

Treatment of syndromes other than secondary depression in the course of schizophrenia with adjunctive antidepressant medication have not been well investigated. Although 'negative symptoms', for example, appear to respond in some cases where there is an overlap with depression (Bucci, 1987; Siris *et al*, 1991), this issue has not been thoroughly examined in non-depressed schizophrenic patients, despite a preliminary positive double-blind trial (Silver & Nassar, 1992) and some open clinical evidence that this may be the case (Goff *et al*, 1990; Bodkin, J. A., personal communication). Similarly, although case reports exist of an adjunctive tricyclic antidepressant being helpful in schizophrenic patients who present with a clinical phenocopy of panic disorder (Siris *et al*, 1989*a*), and adjunctive clomipramine being beneficial to such patients with obsessive–compulsive-type symptomatology (Stroebel *et al*, 1984), conclusive double-blind clinical trials concerning these issues during maintenance-phase treatment have not been published.

The large majority of double-blind studies examining antidepressant medication in schizophrenia have involved tricyclic antidepressants rather than monoamine oxidase (MAO) inhibitors (Brenner & Shopsin, 1980; Siris, 1991). One double-blind MAO-inhibitor study focusing on negative symptoms in patients with 'depressive syndrome superimposed on residual schizophrenia', however, did show apparent efficacy over time (Bucci, 1987), and an encouraging preliminary trial with L-deprenyl, an MAO-B inhibitor, has been reported (Bodkin, J. A., personal communication). This is an issue which may have heuristic as well as clinical relevance, and further trials are indicated.

Adjunctive lithium

Relatively few controlled studies have been reported of the use of lithium treatment in schizophrenia (as opposed to schizoaffective disorder), and most of these have involved acute treatment of psychotic episodes (rather than maintenance-phase treatment) (Christison *et al*, 1991). The larger body of these

reports suggests, however, that lithium use may confer at least some benefit to between a third and a half of schizophrenic patients, so it is not a drug whose use should be ignored in this population (Small *et al*, 1975; Carmen *et al*, 1981; Delva & Letemendia, 1982; Christison *et al*, 1991). The most frequent predictor of favourable response to the addition of lithium has been reported to be excitement (including angry excitement), overactivity, and euphoria (issues, obviously, which are more relevant to acute treatment than to maintenance treatment), but depressive symptoms have also been noted to be a positive prognosticator of favourable response to adjunctive lithium (Lerner *et al*, 1988). Episodic course, previous affective episodes, and family history of affective disorder may also be positive prognostic indicators for the use of adjunctive lithium (Atre-Vaidya & Taylor, 1989). Nevertheless, it has also been noted that the improvement which schizophrenic patients experience in response to adjunctive lithium is likely to be general, including global ratings, thought disorder, hallucinations, delusions, and comprehensive functional capacities, rather than being confined to the realm of affective regulation (Small *et al*, 1975; Delva & Letemendia, 1982; Donaldson *et al*, 1983; Zemlan *et al*, 1984), and, indeed, the opportunity for improvement apparently does not require the presence of affective symptoms at all (Christison *et al*, 1991). Furthermore, adverse psychiatric reactions to the addition of lithium to neuroleptic medication are not evident in the literature, so this would be a reason to withhold a potential therapeutic trial of adjunctive lithium in maintenance-phase patients who were doing less well than might be hoped.

The possible adverse reaction to lithium, which has frequently been discussed in the literature concerning its combination with neuroleptic agents and/or its use in schizophrenia, is the emergence of neurotoxicity (Gerbino *et al*, 1978). It has been found that phenothiazines increase intracellular lithium concentrations, and this has been suggested as a mechanism contributing to neurotoxicity (Cooper, 1987), especially in the light of higher neuroleptic doses appearing to predispose to occasional cases of reversible lithium-induced delirium at therapeutic lithium plasma levels (Miller & Menninger, 1987). Nevertheless, controlled investigations have generally failed to confirm this event as an important danger beyond the ordinary risk of lithium toxicity in patients not receiving neuroleptics (Delva & Letemendia, 1982; Donaldson *et al*, 1983), and specifically the single early report implicating a particular risk to the haloperidol–lithium combination (Cohen & Cohen, 1974) has not been substantiated (Cooper, 1987). Of course, it remains an important component of adjunctive lithium treatment carefully to monitor blood levels during the course of treatment. In the absence of adverse effects, these plasma levels should be maintained in the usual prophylactic range (0.7–1.2 mmol/ml) (Delva & Letemendia, 1982). Over the longer term, among patients continued on adjunctive lithium because an initial trial has indicated benefit, kidney and thryoid function should also be monitored, as it would be in any other lithium-maintenance patient. Long-term studies of the use of lithium with neuroleptics have not been undertaken, so it is not known if lithium ultimately impacts on the required neuroleptic dosage, or if there are other issues which might affect cumulative longitudinal toxicity.

Carbamazepine

The one double-blind study to have been reported to date utilising carbamazepine in the maintenance phase of the treatment of schizophrenia used carbamazepine alone rather than in conjunction with a neuroleptic (Carpenter *et al*, 1991). Although the results of this study were negative, they do not address the issue of the utility of carbamazepine as an adjunctive agent – a situation which may be more promising on the basis of double-blind acute-treatment studies, four out of five of which have indicated a positive impact (Neppe, 1983; Klein *et al*, 1984; Kidron *et al*, 1985; Dose *et al*, 1987; Okuma *et al*, 1989). Suggested potential positive prognostic indicators for adjunctive carbamazepine include psychomotor overactivity (Christison *et al* 1991), excitement (Klein *et al*, 1984; Okuma *et al*, 1989), violence (Hakola & Laulumaa, 1982; Neppe, 1983; Yassa & Dupont, 1983; Luchins, 1984) and electroencephalogram abnormalities (Neppe, 1983). If carbamazepine is utilised in this way, it should be borne in mind that carbamazepine can lower plasma neuroleptic levels, and it may therefore be valuable to monitor neuroleptic levels as well as carbamazepine levels in patients (Kidron *et al*, 1985; Kahn *et al*, 1990). The modal studies reported have utilised carbamazepine in the plasma concentration range of 8–12 μg/ml. Additionally, patients receiving carbamazepine should be monitored regularly for the possibility of agranulocytosis and liver-function abnormalities. Caution is also advised when discontinuing adjunctive carbamazepine in these patients, since sudden discontinuation has occasionally been accompanied by clinical deterioration (Dose *et al*, 1987; Heh *et al*, 1988).

Discussion

The proper focus for the maintenance treatment of schizophrenia is now at a point where it can progress beyond the simple suppression of psychotic symptoms with neuroleptic medication and the management of obvious neuroleptic side-effects. At this point, we are in a position to address other longitudinal-treatment targets having to do with the enhancement of functional capacities and quality of life, and our treatment approaches need to be examined in the context of this challenge (GAP, 1992).

In that light, this paper has reviewed the most commonly employed adjunctive-medication regimens used in the long-term management of neuroleptic-maintained schizophrenia: anti-Parkinsonian agents, benzodiazepines, propranolol, antidepressants, lithium, and carbamazepine. Other medication may also be utilised adjunctively, although there is, to date, less literature devoted to the appropriate roles of these agents. They include clonidine (Donaldson *et al*, 1983; Bond, 1986; Adler *et al*, 1987*a*; Fleischhacker *et al*, 1990), other alternative beta-blockers (Johnson, 1984), sodium valproate (as a possible substitute for carbamazepine), reserpine (Christison *et al*, 1991), methadone (Siris, 1990), disulphiram (Siris, 1990), bromocriptine (Levi-Minzi *et al*, 1991), L-dopa (Meltzer *et al*, 1986; Christison *et al*, 1991) and amphetamine (Angrist *et al*, 1982; Cesarec & Nyman, 1985; Meltzer *et al*, 1986; van Kammen & Boronow, 1988). Purely from a treatment perspective, each adjunctive compound has potential drawbacks (as noted above) which need to be considered. These include pharmacokinetic interactions with needed neuroleptic medication, adverse pharmacodynamic interactions, and side-effects of the adjunctively used agents themselves. Each of these effects may contribute to non-compliance, cause morbidity, and/or otherwise complicate the patient's clinical picture.

In addition to its purely practical utility, related to the possible symptomatic and functional benefits to be derived, the use of such adjunctive medication generates the implication that a meaningful diagnostic strategy may evolve for guiding these adjunctive pharmacotherapeutic practices. It is even possible that the diagnostic categories generated might be of value in understanding the clinical heterogeneity of schizophrenia. One strategy for approaching such a diagnostic nosology of schizophrenic patients in the maintenance treatment phase involves the identification of specific secondary syndromes which can occur in the long-term course of schizophrenia (Siris, 1988). These specific secondary syndromes, which might often contribute to so-called 'negative symptom' states or other phenotypic expressions of 'failure to thrive', could then be targeted by appropriate specific adjunctive remedies.

The specific syndromes of akinesia and akathisia, although potentially easy to miss in their more subtle manifestations, are already well known. Traditionally they have been considered under the rubric of neuroleptic side-effects, although the vulnerabilities to these manifestations may, in fact, involve processes intrinsic to the patients themselves. Indeed, the phenomenological similarities between akinesia and 'negative symptoms' (Bermanzohn & Siris, 1992) as well as the hypodopaminergic (Meltzer, 1985; Carlsson, 1988; Reynolds, 1989; Davis *et al*, 1991) and cholinergic (Tandon & Greden, 1989) hypotheses of negative symptoms support this outlook. In particular, the hypodopaminergic hypothesis of negative symptoms, along with the suggestion that blockade or hypofunction of dopamine systems could be involved in the inhibition of pleasure or the generation of dysphoric states such as depression (Galdi *et al*, 1981; Wise, 1982), reinforces the notion that maintenance-phase neuroleptic-treated schizophrenic patients might sensibly be looked at as a meaningful population worthy of study in its own right.

Within such a population, secondary syndromes might be identified, recognisable by their psychiatric stigmata. Although the exact relationship (if, indeed, there necessarily is one) of these secondary syndromes to the biological pathophysiology of schizophrenia itself is as yet unclear, treatment approaches to these secondary syndromes could be informed by what we already know about these syndromes when they occur in other contexts. Appropriate adjunctive interventions could then be undertaken when schizophrenic patients appeared to manifest such secondary syndromes as depression, cyclothymia, generalised anxiety, panic, post-traumatic stress, obsessive–compulsive symptomatology, or substance abuse.

Unfortunately, the studies which exist to date in the literature have rarely taken this syndromal approach to the use of adjunctive medication in schizophrenia. Although there have been exceptions (Kellner *et al*, 1975; Siris *et al*, 1987), patients have most often been entered into treatment trials without such strategy of syndromal targeting. This is an approach which may have predisposed to Type II errors. A complementary and potentially fruitful research strategy, which has largely been ignored in this arena of work, is the identification of apparently responsive individuals, who are then re-subjected to subsequent trials under vigorously controlled conditions. Such a strategy could be very helpful in a condition such as schizophrenia which is considered to be intrinsically heterogeneous.

Beyond the simple reduction of symptoms and morbidity associated directly with various secondary syndromes, it is possible that appropriate adjunctive treatment may reduce specifically schizophrenic symptoms as well, consistent with the stress–diathesis model (Zubin & Spring, 1977; Neuchterlein & Dawson, 1984). This possibility can readily be conceptualised when the stress–diathesis model is considered in the context of evidence that the underlying biological vulnerability to schizophrenia constitutes a continuum–from a smaller group of individuals with an exceptionally high inherent vulnerability, to a much larger group with lower levels of vulnerability (Weinberger, 1987). Within this model, some individuals have such a high 'dose' of the diathesis for schizophrenia that it inevitably becomes manifest regardless of other factors. Another, larger, group of individuals, however, has a more marginal dose of the diathesis, such that it is likely to become manifest only in the presence of one or more of the various additional biopsychosocial insults which research and/or clinical description have indicated are associated with the occurrence of schizophrenia. These include birth trauma, intrauterine or other early-life viral infection, toxic exposure, poor nutrition, psychodynamic vulnerabilities resulting from untoward early life experiences, poverty and social deprivation, medical illnesses, other acute or chronic major stresses during the age of risk, or substance abuse. In the context of this stress–diathesis model, the presence of a second psychiatric syndrome could also constitute an important non-specific stressor, predisposing to the expression of psychotic symptomatology (Siris, 1988). The prevalence of patients 'recruited' from the pool of those with a second psychiatric diathesis would not be trivial, since a much larger population of patients with a marginal version of the schizophrenia diathesis would then be at risk. In keeping with this hypothesis, treatment of such a second syndrome could reduce the stress associated with that syndrome, and thereby lessen the propensity for psychosis among vulnerable individuals.

Unfortunately, in many areas, conclusive double-blind placebo-controlled trials have not as yet been performed which would test the hypotheses of this model. Nevertheless, most of the data which are available suggest that the adjunctive interventions which would be indicated by this approach appear to have favourable benefit/risk ratios when trials are undertaken with reasonable cautions and in the appropriately selected populations. These agents are therefore suitable for individual, carefully considered, patient by patient trials clinically, as well as for larger controlled studies.

There is, of course, no guarantee about the eventual degree to which the strategy of searching out and treating secondary syndromes in the neuroleptic-maintenance phase of schizophrenia will be successful. Certainly, not every patient will have such an identifiable syndrome, and certainly not every patient with an identifiable syndrome will respond. On the other hand, if we do not look for these syndromes, we will be unlikely to notice them in the situations where they might occur and then to furnish our patients with the opportunity to respond to the related adjunctive interventions. Moreover, on a more heuristic level, the strategy of searching out secondary syndromes and applying adjunctive-treatment strategies is subject to empirical testing and validation from both the psychopharmacological and pathophysiological perspectives. It may therefore constitute a useful scheme for organising and understanding some aspects of the heterogeneity in the longitudinal presentation of schizophrenia, as well as informing our models concerning the approaches to its treatment.

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Samuel G. Siris, MD, *Director of Adult Psychiatric Day Programs, Hillside Hospital Division of the Long Island Jewish Medical Center, and Professor of Psychiatry, Albert Einstein College of Medicine, 75-59 263rd Street, Glen Oaks, NY 11004, USA*