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REVIEW

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A meta-analysis of the response to chronic L-dopa in patients with schizophrenia: therapeutic and heuristic implications

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Abstract *Rationale:* While it is generally believed that administration of the dopamine precursor levodopa (L-dopa) exacerbates symptoms of schizophrenia, numerous reports suggest that adjunctive L-dopa may be beneficial. This body of literature has not been critically reviewed. *Objectives:* On the basis of published studies, to determine whether L-dopa administered concomitantly with antipsychotic drugs provides a beneficial response in patients with schizophrenia. *Methods:* This review examined 30 studies involving 716 patients. Due to wide methodological variability and limited statistical information, only five studies encompassing 160 patients could be included in a meta-analysis. The others were evaluated qualitatively. *Results:* When L-dopa was added to antipsychotic drugs, the overall improvement was moderate (d=0.71) and highly significant (P<0.0001). There were 16 other studies in which L-dopa was added to antipsychotic drugs, but which did not meet criteria for inclusion in the meta-analysis. In these, worsening occurred in less than 20% of patients; the percentage of improved patients varied widely but had a central tendency around 50%. *Conclusions:* In patients already on antipsychotic drugs, the addition of L-dopa can be beneficial. Dopamine agonists merit further consideration as adjuncts to antipsychotic drugs in the treatment of schizophrenia.

Keywords -Dopa · Schizophrenia · Meta-analysis · Antipsychotic drugs

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Introduction

The classical dopamine (DA) hypothesis holds that certain symptoms of schizophrenia are mediated by increased limbic DA transmission (Mathysse 1972). It was generated by two early observations. The first, that all clinically effective antipsychotic drugs (APDs) block DA receptors, endures to this day (Seeman and Tallerico 1998; http://kidb.bioc.cwru.edu/pdsp.php). The second, that DA agonists exacerbate psychotic symptoms in patients with schizophrenia, has been less consistently supported. The effects of the DA precursor L-dihydroxyphenylalanine (L-dopa) provide a case in point. Published reports describe L-dopa administration to over 700 patients with schizophrenia (Table 1). Of these, a small number of studies are often cited as evidence that L-dopa unequivocally exacerbates psychosis in schizophrenia (Lehrman and Sharav 1997). Yet L-dopa had also been recommended as an adjunct to typical APDs in treatment resistant patients, particularly in those with negative symptoms (Andreasen 1985; Meltzer et al. 1986; Pidgeon and Wolf 1989; Meltzer 1992; Wolkowitz 1993). Several factors may account for this inconsistency. Many L-dopa studies were reported in the non-English literature and were conducted before the implementation of rigorous research designs. Significant methodological differences between studies precluded easy comparisons. Further-

Table 1 Studies of chronic L-dopa use in schizophrenia. *AIMS* Abnormal Involuntary Movements Scale, *APD* antipsychotic drug, *BPRS* Brief Psychiatric Rating Scale, *CGI* Clinical Global Inventory, *clin* clinical diagnosis, *CPZ* chlorpromazine, *DSM* Diagnostic and Statistical Manual, *EPS* extrapyramidal symptoms, *imp* improve, *no ch* no change, *NA* not available, *NOSIE* Nurses's Observation Scale for Inpatient Evaluation, *PANNS* Positive and Negative Syndrome Scale, *PRS* Psychiatric Rating Scale, *+veSx* positive symptoms. *—veSx* negative symptoms, *Scale* other rating scale, *TD* tardive dyskinesia. Note that the three studies mentioned in Asano et al. (1973) are labelled a, b and c, but refer to the same paper

Author/year	Patient sample	Design	L-Dopa dose in mg/day duration	Concurrent APD status	Measurements	Results/comments
Alpert et al. (1978)	*n*=15, (L-dopa=8), age 15–47	Randomized single blind, (8) L-dopa vs (7) CPZ	6000, 24days	Off APD unknown duration	BPRS	Worse-1/no ch-7/impr-0 (L-dopa) L-dopa slightly <CPZ
Angrist et al. (1973)	*n*=10, age 28–50	5–10 days, placebo run-in open	3000–6000, 21 days	Off APD 7 days	BPRS, CGI	Worse-10 Increase in agitation, other +veSx
Asano et al. (1973a)	*n*=9, age 28–65, +ve response to L-dopa	Single blind placebo cross-over	900, 3–5 months	On APD	Clin. somatic Sx	Worse-0/no ch-1/impr-8 (L-dopa) worse-6/no ch-3/impr-0 (placebo)
Asano et al. (1973b)	*n*=12, age 32–61, EPS	Open	600–1200, 8 weeks	On APD	Clin	Worse-1/no ch-11/impr-0
Asano et al. (1973c)	*n*=17, age 28–65, hypochondriac Sx	Open	900, 4 weeks	On APD	Clin, somatic Sx	Worse-0/no ch-2/impr-15
Beramendi et al. (1980)	*n*=31, age 20–62, chronic inpatients	Randomized single blind, placebo	1500+carbidopa 150, 80 days	Off APD	BPRS	L-Dopa worse-2/no ch 3/impr –5 placebo, APD—insufficient information
Brambilla et al. (1979)	*n*=6, age 27–55, hebephrenic, poor prognosis	Open	2000+carbidopa 200, 15 days	Off APD unknown duration	Scale	Worse-0/no ch 4/impr-2
Buchanan et al. (1975)	*n*=28, (L-dopa=14), age 43–65, chronic	Double blind placebo controlled	≤1250, >6 weeks	On APD	Scale	Worse-1/no ch −5/impr-8 (L-dopa) worse-3/no ch-11/impr-0 (placebo)
Calil et al. (1977)	*n*=3, age 24–41, resistance to APD	Open	500, 5 days to 6 weeks	On APD	BPRS	Worse-2/no ch-1
Chouinard and Jones (1987)	*n*=50 (L-dopa=26), age 26–63, EPS	Double blind placebo controlled	265, 6 months+ benserazide)	On APD	BPRS	Worse-0/no ch-26/impr-0 (L-dopa) worse-0/no ch-24/impr-0 (placebo) trend to impr EPS in L-dopa group
Davidson et al. (1987)	*n*=28, age 22–61	Single blind, no placebo	1000, 7 days (carbidopa-100)	Off APD 7 d	BPRS	Worse-6/no ch-22/impr-0 12 pt inc in BPRS in 6/28, inc in both +ve and −veSx
Fleming et al. (1970)	*n*=6, (L-dopa=3), age NA	Double blind placebo controlled	3000–5000, 47 days	On APD	Clin	Worse-1/no ch-0/impr-2 (L-dopa) worse-0/no ch-3/impr-0 (placebo)
Garfinkel and Stancer (1976)	*n*=1, age 53, catatonia	Open	7000, 3 months	Off APD	Clin	Worse-0/no ch-0/impr-1
Gerlach and Luhdorf (1975)	*n*=13, age 25–35, simple schizophrenia	Double blind placebo cross-over	≤900, 12 weeks (+benserazide)	On APD	Clin	Worse-1/no ch-5/impr-7 (L-dopa) worse-2/no ch-9/impr-2 (placebo)
Inanaga et al. (1971)	*n*=3, age 20–26	Open	400–1200, 12–18 months	On APD	Clin	Worse-0/no ch-0/impr-3 Both +ve and −veSx impr
Inanaga et al. (1972)	*n*=84, age 20–51, −veSx	Open	400–600, 1–12 weeks	On APD	Scale	Worse-5/no ch 34/ impr 45
Inanaga et al. (1975a)	*n*=104, (L-dopa=52), age 20–60, −veSx	Double blind placebo controlled	300–600, 8 weeks	On APD	PRS	Worse-2/no ch-24/impr-26 (L-dopa) worse-0/no ch 33/impr-19 (placebo)
Inanaga et al. (1975b)	*n*=5, age 24–54	Open	300–400, 6 weeks–5 months	On APD	Clin	Worse-0/no ch-2/impr-3
Kai (1976)	*n*=8, age 34–49, −veSx	Open	200, 12 weeks	On APD	Scale	Worse—0/no ch-0/impr-8
Kawamura et al. (1971)	*n*=18, av. age 31.1, −veSx	Open	2400–3000, 4 weeks	On APD	Clin	Worse-2/no ch-11/impr-5

Table 1 (continued)

Author/year	Patient sample	Design	L-Dopa dose in mg/day duration	Concurrent APD status	Measurements	Results/comments
Kay and Opler (1985)	*n*=1, age 55, resistant −veSx	Double blind placebo controlled reversal	750, 8 weeks (+carbidopa)	On APD	BPRS PANSS	Neg Sx impred with no change in +ve Sx on L-dopa, no ch on placebo
Ludatscher (1989)	*n*=60 (L-dopa=35), age 29–75, TD	Double blind placebo controlled	500, 12 months (+carbidopa)	On APD	AIMS, clin	Worse-0/no ch-35/impr-0 (L-dopa) worse-0/no ch-25/impr-0 (placebo) reduction in TD by L-dopa
Nishikawa et al. (1972)	*n*=12, age 19–47, resistant −veSx	Open	300–600, 35 days	Off APD for 7 days	Scale	Worse-2/ no ch-5/impr-5 effective in patients sick <10 years
Ogura et al. (1974)	*n*=94, av. age 33.2, resistant to APD	Open	150–1200, 2–72 weeks, mean=18 weeks	On APD	Scale	Worse-4/no ch-69/impr-21 Impr social relatedness > than +ve Sx
Otsuka et al. (1974)	*n*=22, age 17–65	Open	200–750, duration NA	On APD	Clin	Worse-4/no ch-7/impr-11
Sarai et al. (1973)	*n*=35, age 15–52, EPS	Open	200–400 ≥21 days	On APD	Scale	Worse-5/no ch-12/impr-18
Yamauchi (1972)	*n*=30, age 19–51	Open	300–400, ≥60 days	On APD	Clin	Worse-0/no ch-11/impr-19
Yamauchi (1976)	*n*=10, age 24–48	Open	300–600, 8 weeks	On APD	Scale	Worse-1/no ch 7/impr 2
Yaryura-Tobias et al. (1970a)	*n*=4, age 31–53, EPS	Open	1400–2600, 8–23 days	On APD	BPRS/ NOSIE	Worse-4/no ch-0/impr-0, taken off antiparkinsonian agents acutely
Yaryura-Tobias et al. (1970b)	*n*=5, age 27–56, APD responsive	Open	2000, 3 weeks	On APD	Clin	Worse-4/no ch-0/impr-1 impr alertness and communication

more, the widespread availability of atypical APDs has reduced interest in adjunctive treatments, particularly in those from the typical APD era. However, even atypical APDs may only partially treat the cognitive impairments and negative symptoms of schizophrenia (Chakos et al. 2001); these have been linked to deficient cortical DA transmission (Berman and Weinberger 1990; Callicott et al. 2000; Perlstein et al. 2001) and may constitute limiting factors for outcome (Green et al. 2000; Gold et al. 2002; Hoffman et al. 2003). Indeed, if satisfactory clinical outcome is redefined to include psychosocial rehabilitation and integration, then a significant number of patients await improved therapies (Kapur and Remington 2001). Such considerations prompted this review of the chronic use of L-dopa in schizophrenia.

In a few early investigations, high doses of L-dopa administered to patients with schizophrenia, in some cases after abrupt discontinuation of APDs, were reported to exacerbate or induce psychosis (Yaryura-Tobias et al. 1970a, 1970b; Angrist et al. 1973). In contrast, more numerous reports indicated that L-dopa administered concurrently with APDs improved clinical outcome in schizophrenia (Table 2). Thus, the literature suggested that APD status was a critical variable in the response to L-dopa and hence that the following hypotheses should be tested: 1) In APD-free patients, L-dopa is more likely than placebo to be associated with clinical worsening, 2) in APD-treated patients, L-dopa is more likely than placebo to be associated with clinical improvement.

Table 2 Methodological differences between studies. *Sx* symptoms, *APDs* antipsychotic drugs

Design	Studies	Patients
Open	18	378
Double blind	5	202
Single blind	4	74
Placebo	8	261
Formalized rating scales	17	527
Selection of negative Sx	6	230
Concomitant APDs	22	573
Formal Diagnostic Criteria	6	124
Total	27	654

Materials and methods

We conducted a computer based literature search (PubMed online, National Library of Medicine, Bethesda, Md., USA) using the keyword combinations "L-dopa AND schizophrenia" and "L-dopa AND psychosis" from 1965 through July 1 2003. All identified articles were screened and relevant references within those sources were also obtained (Table 1). Native speakers translated foreign-language articles. The initial minimal inclusion criteria for reports were: a) included adult subjects with schizophrenia, b) described or measured psychiatric response, c) treated subjects for at least 5 days with L-dopa, d) reported in a peer-reviewed journal. Upon further examination, we excluded all single-case reports (Garfinkel and Stancer 1976; Kay and Opler 1985), a report in which patients received L-dopa concomitantly with a monoamine oxidase inhibitor (Turner and Merlis 1964), as well as reports (Inanaga and Tanaka 1973; Gutierrez et al. 1979) in which the same subjects had been described in earlier publications (Inanaga et al. 1972; Beramendi et

Table 3 Meta-analysis of L-dopa treatment effect when L-dopa was added to antipsychotic drugs in patients with schizophrenia. The effect sizes (*d*) are significantly heterogeneous [$Q(4)=24.411$ $P<0.001$]. Mean $d=1.58$, total $n=160$, total n/studies=32

Study	*d*	*P*
Buchanan et al. (1975)	1.5854	0.0002
Inanaga et al. (1975a)	0.2722	0.1670
Asano et al. (1973)	3.6129	0.0000
Fleming et al. (1970)	1.6000	0.0774
Gerlach and Luhdorf (1975)	0.8275	0.0366
Overall	0.7116	0.0000

al. 1978). We also excluded one study of L-dopa effects on tardive dyskinesia because information on psychopathology in 60 patients was limited to the comment "No exacerbation of the psychosis was observed" (Ludatscher 1989). In contrast, we included other studies in which authors were primarily interested in L-dopa effects on tardive dyskinesia or extrapyramidal symptoms but also assessed psychiatric symptoms (Yaryura-Tobias et al. 1970b; Kawamura 1971; Sarai et al. 1973; Chouinard et al. 1987). In the one case where three independent studies were described in a single report (Asano et al. 1973), we considered the studies independently and have referred to them as a, b and c in the tables.

In total, 27 reports describing a total of 654 patients were included. Of the former, eight were in Japanese, one in Spanish and the remainder in English. The following information was extracted from each article: i) demographic data, ii) diagnostic criteria/selection methods, iii) L-dopa dose, duration of treatment, iv) concurrent medications, v) study design, vi) method for determination of psychiatric changes, vii) basis for conclusions (e.g. statistical analysis versus clinical impression). The approximate equivalence between the centrally active dose of L-dopa with and without a dopa-decarboxylase inhibitor was accepted as 4:1 (Cedarbaum 1987).

There was considerable methodological variability between the studies (Table 2). Although most used formal rating scales of psychopathology, some of the scales were symptom based (e.g. Brief Psychiatric Rating Scale), while others consisted of a single global score. Several reports provided only the direction of change in an overall score but neither its magnitude nor changes in individual factors. In view of such heterogeneity, we adhered as closely as possible to the approach used in each report for the assignment of outcome. For instance, when the BPRS was used but the actual BPRS scores not provided, we accepted the conclusions of the investigators as to the fraction of patients who improved and those who showed worsening (e.g. Angrist et al. 1973). When individual patient scores were provided, we adopted the investigators' definition of significant response (e.g. 12-point change in BPRS) (Davidson et al. 1987).

Placebo-controlled studies in which treatment with APD+L-dopa could be compared to treatment with APD alone were subjected to meta-analysis (DSTAT). For the purposes of the meta-analysis, patients were assigned to one of two response groups; Poor response=no change or worsening, Good response=improved. More specifically, within the L-dopa+APD and the APD only groups in each study, each subject with a Poor response was assigned a value of "0" and a "1" was assigned to each subject with a Good response. Within-group variance and pooled variance were calculated using standard formulae. The effect size ($P_{Ldopa+APD}-P_{APD})/SD_{pooled}$) for each study was converted to *r*, which was tested for significance using a one-tail *t*-test with the *df*s associated with the correlation (N1+N2–2). These *P*-values are presented in Table 3, along with the corresponding effect sizes (*d*) and probability. The outcomes across the five studies were combined by averaging the *d*-values (effect sizes) (Rosenthal and Rosnow 1991), with each *d* weighted by the reciprocal of its variance. This procedure gives greatest weight to the most reliably estimated study outcomes, those with the largest sample sizes (Hedges and Olkin 1985).

Other reports were evaluated qualitatively. For studies in which L-dopa was openly added to patients already on APD, we constructed a table and plotted the number of subjects against the percentage who definitely improved or showed definite worsening in each study. For studies in which L-dopa was administered without concomitant APDs, all the patients were pooled and the overall percentage of patients who had definite clinical worsening was determined.

Results

The 27 studies involving 654 patients (Table 2) showed considerable heterogeneity of design, patient age (15–75 years), daily L-dopa dose (150–7000 mg), and duration of treatment (5 days to 18 months). Approximately 40% of all patients ($n=261$) were enrolled in double blind studies with a placebo control. For the majority of patients ($n=530$), diagnosis was based on clinical impression but outcome was determined on some formal scale ($n=527$).

There was no placebo-controlled study in which L-dopa was administered to APD-free patients. Similarly, there was no study in which L-dopa in combination with APDs was compared to L-dopa administration alone. In contrast, there were five placebo-controlled studies in which L-dopa was added to APD-treated patients ($n=160$) (Fleming et al. 1970; Asano et al. 1973; Buchanan 1975; Gerlach and Luhdorf 1975; Inanaga et al. 1975a), and which could be subjected to meta-analysis. While the effect sizes (Cohen's *d*) for the L-dopa response (Table 3) were very heterogeneous, ranging from 0.27 (Inanaga et al. 1975a) to 3.6 (Asano et al. 1973), all were in the same direction. The overall composite effect size was 0.71 (between medium and large) and highly significant ($P<0.00001$). With only five studies, it was not possible to determine the source of heterogeneity. [Note: in the study with the greatest effect size (Asano et al. 1973), patients had been selected on the basis of a previous good response to open administration of L-dopa. If that study is excluded, the overall effect size becomes 0.59, still in the medium to large range, and remains highly significant, $P<0.0003$].

There were 16 non-placebo controlled studies in which L-dopa was added to patients already on APDs (Table 4). A plot of the percentage of those who improved against sample size showed that studies with a small sample size had a wide range of improvement with a central tendency around 50% (Fig. 1). A plot of sample size against the percentage of those who showed worsening demonstrates that in 13 studies, less than 20% of the patients showed worsening (Fig. 2); all three studies in which over 20% of patients worsened (Yaryura-Tobias et al. 1970a, 1970b; Calil et al. 1977) had very small patient samples ($n\leq4$). A total of 64 patients in five studies received L-dopa without concomitant APDs; 38% of the latter showed definite worsening (Angrist et al. 1973; Alpert et al. 1978; Brambilla et al. 1979; Beramendi et al. 1980, Davidson et al. 1987).

Table 4 Open studies in which L-dopa was added to patients on antipsychotic drugs but which did not meet criteria for inclusion in the meta-analysis. *n*=number of patients. Note that the three studies mentioned in Asano et al. (1973) are labelled a, b and c, but refer to the same paper

Study	*n*	*n* better	*n* worse	% better	% worse
Asano et al. (1973b)	12	0	1	0	8
Asano et al. (1975c)	17	15	0	88	0
Calil et al. (1977)	3	0	2	0	67
Inanaga et al. (1971)	3	3	0	100	0
Inanaga et al. (1972)	84	45	5	54	6
Inanaga et al. (1975b)	5	3	0	60	0
Kai et al. (1976)	8	8	0	100	0
Kawamura et al. (1971)	18	5	2	28	11
Nishikawi et al. (1972)	12	5	2	42	17
Ogura et al. (1976)	94	21	4	22	4
Otsuka et al. (1974)	22	11	4	50	18
Sarai et al. (1973)	35	18	5	51	14
Yamauchi et al. (1972)	30	19	0	63	0
Yamauchi et al. (1976)	10	2	1	20	10
Yaryura-Tobias et al. (1970a)	4	0	4	0	100
Yaryura-Tobias et al. (1970b)	4	0	4	0	100
Mean	–	–	–	42.4	22.2
Median	–	–	–	45.8	9.2

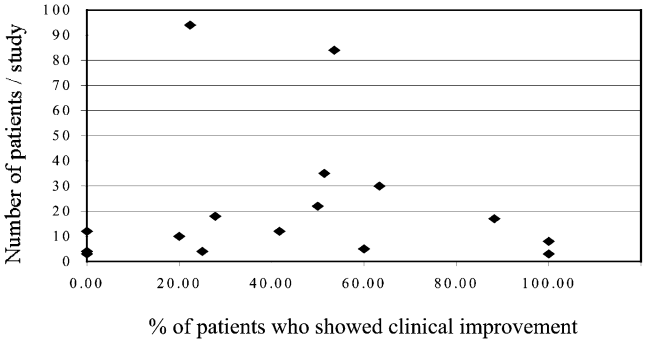

Fig. 1 Plot of number of patients per study against the percentage of patients on typical APDs who improved during L-dopa treatment

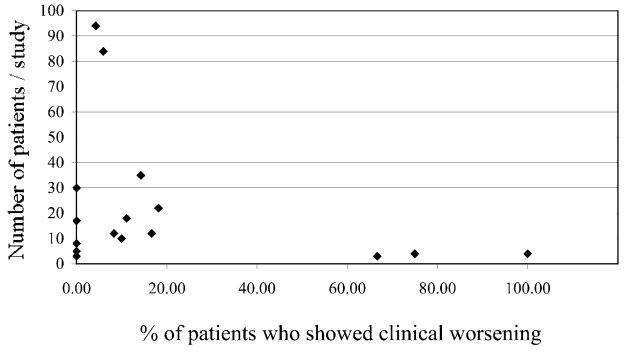

Fig. 2 Plot of number of patients per study against the percentage of patients on typical APDs who showed worsening during L-dopa treatment

Discussion

We could not determine whether chronic L-dopa administration was more likely than placebo to cause worsening in APD-free patients. On the other hand, a meta-analysis showed that administration of L-dopa to patients concomitantly treated with APDs was associated with significant improvement. These statements must be understood within methodological limitations.

First, only a fraction of published studies (*n*=5/30, patient *n*=160/716) met criteria for inclusion in our meta-analysis. There was no placebo-controlled study in which chronic L-dopa was administered to APD-free patients with schizophrenia. While 38% of the pool of all APD-free patients treated with L-dopa had definite clinical worsening, the latter is mitigated by several considerations. All those patients received high doses (>1000 mg/day) of L-dopa, often after abrupt cessation of APDs (Angrist et al. 1973; Alpert et al. 1978; Brambilla et al. 1979; Beramendi et al. 1980, Davidson et al. 1987). Schizophrenia and particularly untreated schizophrenia are per se associated with an increased risk of exacerbation. Over a 10-month period, the general estimated prevalence of exacerbation in schizophrenia is 16% in APD-treated individuals but 56% in patients who are not taking APDs (Gilbert et al. 1995). The majority (84%) of patients in the current review who received L-dopa without concomitant APDs did so for less than 4 weeks (Angrist et al. 1973; Alpert et al. 1978; Brambilla et al. 1979; Beramendi et al. 1980; Davidson et al. 1987). Furthermore, insofar as L-dopa increases verbal communicativeness (Yaryura-Tobias et al. 1971), rating scales that depend on self-reporting of symptoms may overestimate the emergence of psychotic symptoms in the previously withdrawn patient. Thus the true risk of psychotic exacerbation associated with L-dopa administration to APD-free patients cannot be reliably determined. Our data do not refute, however, the possibility that APD-free patients with schizophrenia may be more vulnerable to L-dopa induced exacerbation than other psychiatric groups. In non-psychotic psychiatric conditions (e.g. major depression), the appearance of psychotic symptoms during L-dopa treatment tends towards the lower range of 0–15% of patients (Sathanathan et al. 1973; Dunner and Fieve 1975; Mendels et al. 1975; Shingu et al. 1979; Oren et al. 1994), but may be higher in

patients with a psychotic affective illness (Bunney et al. 1971)

Our main goal was to determine whether adding L-dopa to APDs is beneficial; the overall L-dopa effect (0.71) suggests that it is moderately so. Unfortunately, the impact of L-dopa on individual symptoms and particularly on positive and negative symptoms could not be determined. While two (Inanaga et al. 1972, 1975a) of four studies which selected for patients with negative symptoms (Kawamura et al. 1971; Inanaga et al. 1972, 1975a; Nishikawa et al. 1972; Kai et al. 1976) considered the latter to be particularly responsive to L-dopa, the majority of studies did not specifically measure such symptoms. Furthermore, since APD-induced extrapyramidal effects can mimic negative symptoms, L-dopa's anti-parkinsonian effects would need to be taken into account. Similarly, we could not analyze factors such as L-dopa dose, duration of treatment or duration of illness. One group posited that a beneficial L-dopa response was confined to patients within 5 years of illness onset (Inanaga et al. 1975b), but this could not be tested overall. It is particularly unfortunate that neuropsychological assessments were not done. L-dopa affects cognition in other neuropsychiatric conditions and cortical DA has been implicated in the cognitive deficits of schizophrenia (Berman and Weinberger 1990; Perlstein et al. 2001).

L-Dopa effects on the brain have been extensively studied. In vivo imaging confirms that exogenous L-dopa is converted to synaptic DA in normal primates (Tedroff et al. 1992) and in patients with Parkinson's disease (Tedroff et al. 1996). In unmedicated patients with schizophrenia, the striatal DA system displays an increased rate of conversion of radiolabeled L-dopa to DA (Reith et al. 1994; Lindstrom et al. 1999), as well as higher concentrations of both baseline (Abi-Dargham et al. 2000) and amphetamine-releasable DA (Breier et al. 1997; Laruelle and Abi-Dargham 1999); the latter have been linked to positive symptoms of schizophrenia (Breier et al. 1997; Laruelle and Abi-Dargham 1999). Thus, any increased risk of psychotic relapse or exacerbation during chronic L-dopa administration in APD-free patients is probably due to L-dopa-induced potentiation of DA release in the limbic striatum.

Endogenous DA competes with DA receptor antagonists for binding to DA receptors. Manipulations that increase or decrease endogenous DA levels, respectively, lower or increase DA antagonist binding to striatal DA receptors in schizophrenia (Breier et al. 1997; Laruelle and Abi-Dargham 1999; Abi-Dargham et al. 2000). Thus the incremental DA released due to L-dopa administration would displace APD from D_1, D_2, D_3 and/or D_4 receptors, depending on the APD profile (http://kidb.bioc.cwru.edu/pdsp.php). If, however, therapeutic actions depend on APD occupancy of DA receptors, how could L-dopa-induced elevation of DA levels lead to improvement rather than to psychotic exacerbation? There are several possibilities.

One recent hypothesis suggests that prolonged DA receptor occupancy is not necessary for APD action (Kapur and Seeman 2001). Indeed, enhanced APD effects may derive from rapid occupancy but quick dissociation of the APD from D_2 receptors. This dissociation occurs more quickly at high DA concentrations (Seeman and Tallerico 1999) and hence could be promoted by optimally elevating synaptic DA levels. Atypical APDs with weak D_2 antagonist properties such as clozapine and quetiapine (Seeman and Tallerico 1998) are of particular interest; both drugs can reduce L-dopa induced psychosis in Parkinson's disease (Meltzer et al. 1995; Trosch et al. 1998; Fernandez et al. 1999) yet are readily displaced from D_2 receptors by endogenous DA (Seeman and Tallerico 1999). The latter raises the possibility that adjunctive L-dopa might be especially useful in patients with schizophrenia who are partial responders to clozapine or quetiapine.

A different mechanism by which elevated DA levels could prove beneficial involves the distinction between tonic and phasic DA release. It has been posited that in schizophrenia abnormally low levels of tonically released striatal DA lead to compensatory upregulation of enzymes of DA synthesis and of postsynaptic DA receptors; the exaggerated effects of phasically released DA are then expressed as positive symptoms (Grace 1991, 1993). Accordingly, maneuvers which increase tonic levels of synaptic DA should blunt the quantity and effects of phasically released DA (Grace 1991, 1993). L-Dopa administration would be expected to increase tonic DA levels; if in addition it did not reverse APD-induced depolarization blockade then co-administration of APD and L-dopa would meet the proposed requirements for enhanced antipsychotic efficacy (Grace 1993).

By definition, DA is a full agonist at all DA receptors. In contrast, partial DA agonists can act as agonists at presynaptic DA receptors and as antagonists at postsynaptic DA receptors; they can reduce net limbic DA transmission but with a lower relative tendency to increase the sensitivity of the postsynaptic DA receptors (for review, see Tamminga and Carlsson 2002). Indeed, such a mechanism may contribute to the therapeutic properties of the recently introduced APD aripiprazole (Burris et al. 2002; Yokoi et al. 2002). Partial agonism can be produced in vitro by combining a full direct agonist with a full antagonist (Ebert et al. 1994). Could partial agonism be achieved in vivo by combining the indirect DA agonist L-dopa with a full DA antagonist? It would require that L-dopa induced changes in DA levels i) enhance stimulation of presynaptic autoreceptors so as to attenuate limbic striatal DA release and/or synthesis, yet ii) be insufficient to markedly displace APD binding to postsynaptic DA receptors. Stimulation of the presynaptic autoreceptor can indeed attenuate the conversion of L-dopa to DA in vivo (Cumming et al. 1995, 1997). Whether the latter could more than offset the increase in DA synthesis attributable to higher L-dopa levels is not known.

Both APDs and L-dopa also affect DA transmission in cortical regions. In the rat, exogenous L-dopa produces a relatively larger and longer lasting increase in DA levels

in the prefrontal cortex than in the striatum (Loeffler et al. 1997); the resulting prefrontal cortex DA levels correlate highly with serum L-dopa levels (Carey et al. 1995). Interestingly, schizophrenia is associated with an increased conversion of administered L-dopa to DA in the prefrontal cortex (Lindstrom et al. 1999). The latter may be compensation for reduced prefrontal cortex DA innervation (Akil et al. 1999) or an attempt at feedback inhibition (Kolachana et al. 1995) of excessive limbic DA release (Breier et al. 1997; Laruelle and Abi-Dargham 1999). In clinical research, the prefrontal cortex, and particularly the D_1 receptors in the prefrontal cortex, have been implicated in working memory deficits, conceptual disorganization (Berman and Weinberger 1990; Perlstein et al. 2001; Abi-Dargham et al. 2002) as well as in the so-called negative symptoms of schizophrenia (Callicott et al. 2000). Given the relative preponderance of D_1 relative to D_2 receptors in cortical regions (Hall et al. 1994), augmentation of prefrontal cortex DA release during APD blockade of D_2 receptors would preferentially increase stimulation of cortical D_1 receptors. Since the DA neurons innervating the prefrontal cortex are resistant to APD-induced depolarization blockade (Chiodo and Bunney 1983; White and Wang 1983; Chen et al. 1992), L-dopa could produce a regionally selective sustained increase in DA levels. Indeed, the co-administration of L-dopa and APDs to patients with schizophrenia could have two functionally linked but regionally distinct beneficial effects. Direct augmentation of deficient limbic cortical DA transmission could improve cognitive deficits and negative symptoms. Furthermore, augmented PFC DA tone would reduce and hence normalize exaggerated effects of phasically released limbic striatal DA, thus attenuating positive symptoms (Grace 1991, 1993). There are other possibilities as well.

Several observations point to the existence of L-dopa specific receptors and suggest that L-dopa may act as a neuromodulator of DA and other systems (Opacka-Juffry and Brooks 1995; Misu et al. 1996). Indeed, L-dopa modulation of striatal DA neurotransmission has been demonstrated in primates in vivo (Tedroff 1997). Exogenous L-dopa can also increase brain noradrenaline synthesis under basal (Kato et al. 1987) as well as drug-stimulated conditions (Dolphin et al. 1976; Nguyen and Angers 1987; Buu 1989). Noradrenaline in turn, has been implicated in the pathophysiology of schizophrenia and in the therapeutic response to antipsychotic drugs (van Kammen and Kelley 1991; Friedman et al. 1999). Such mechanisms might also be involved in L-dopa effects on schizophrenia.

What are the clinical and research implications of our analysis? We conclude that high dose L-dopa should not be administered to APD-free patients with schizophrenia in the absence of a highly compelling reason, and then only with careful clinical and Institutional Review Board supervision. While we could not quantify the risk of exacerbation associated with L-dopa administration to APD-free patients, some risk is likely. At the very least, there is no evidence that administering L-dopa to APD-free patients is therapeutic. The possible role of L-dopa as an adjunct for patients with an inadequate APD response remains to be defined. Three challenges must be met. First, there is the perception that L-dopa administration to patients with schizophrenia is inherently unethical (e.g. Lehrman and Sharav 1997). The latter contention, in its most strident form, is not supported by the scientific data. Second, if the effect of L-dopa could not be adequately defined in studies involving over 700 patients, what justification is there for additional investigations? In this regard, we note that most available studies do not meet modern standards; the abundance of data cannot compensate for this. Third, one could argue that the availability of novel APDs has rendered adjunctive treatments obsolete. Unfortunately, significant symptoms as well as cognitive and psychosocial deficits persist in many patients treated with atypical APDs (Chakos et al. 2001). The latter may be a paradoxical consequence of the success of atypical APDs, insofar as their use has prompted a reappraisal of what constitutes a satisfactory treatment outcome (Kapur and Remington 2001). In this context, consideration of novel therapies, including adjunctive treatments is well justified. The results of our meta-analysis are consistent with studies of other DA agonists (Benkert et al. 1995). We are not recommending that clinicians routinely combine L-dopa with typical or atypical APDs for patients with schizophrenia who are poor or partial treatment responders. Nonetheless, further evaluation of L-dopa and other DA agonists as adjunctive treatments for schizophrenia is certainly warranted.

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