Eur Arch Psychiatry Clin Neurosci (1995) 244:320–324 © Springer-Verlag 1995

ORIGINAL PAPER

K. Ikeguchi · A. Kuroda

Mianserin treatment of patients with psychosis induced by antiparkinsonian drugs

Received: 21 March 1994 / Accepted: 5 October 1994

Abstract We evaluated the effects of mianserin, a relatively selective 5-HT_2 receptor antagonist, on symptoms related to drug-induced psychosis in patients with Parkinson's disease (PD). A total of 12 patients with PD who had developed drug-induced psychosis showed delirium (DSM-III-R criteria; n = 10) and pure visual hallucinations (n = 2). The antiparkinsonian drugs involved in the drug-induced psychosis were L-DOPA/carbidopa, bromocriptine, trihexyphenidyl, and amantadine. They received mianserin (mean 36.7 mg, range 20–60 mg) given orally for 8 weeks. Complete relief or marked improvement in psychotic symptoms was noted in 8 patients, moderate improvement in 2 patients, and no effect in 2 patients. The parkinsonian disability also decreased slightly in 8 patients. These results suggest that serotonin antagonism at 5-HT_2 receptors may not only play an important role in the treatment of drug-induced psychosis in PD, but may also ameliorate the symptoms of parkinsonism.

Key words Parkinson's disease · Drug-induced psychosis · 5-HT_2 receptor · Mianserin · Serotonin

Introduction

Psychosis is a common side effect of the drug administration used to treat patients with Parkinson's disease (PD). The dopaminergic (Celesia and Barr 1970) and anticholinergic (De Smet et al. 1982) properties of antiparkinsonian drugs have been implicated in producing psychosis. Such patients are conventionally treated by a reduction in drug doses, or are given a neuroleptic in addition. However, these methods usually lead to a worsening of their parkinsonian symptoms.

The hallucinations that are observed in drug-induced psychosis in PD have been noted in patients who have abused hallucinogenic agents such as 4-bromo-2,5-dimethoxyphenylisopropylamine (DOB). Most hallucinogens are direct agonists at serotonin-2 (5-HT_2) receptors (Glennon et al. 1984). The majority of neuroleptics act as antagonists at the 5-HT_2 receptors as well as at the dopamine receptors (Meltzer and Nash 1991). Therefore, serotonergic, as well as cholinergic and dopaminergic, mechanisms may be involved in the development of drug-induced psychosis in PD.

We evaluated the effects of the 5-HT_2 receptor antagonist mianserin (Peroutka 1987) on the involvement of the serotonin system in PD patients with drug-induced psychosis.

Subjects and methods

We selected 12 patients with Parkinson's disease (stage III to IV on Hoehn and Yahr scale [Hoehn and Yahr 1967]) who had drug-induced psychosis (caused by L-DOPA/carbidopa, bromocriptine, trihexyphenidyl, or amantadine), which had been continued for 3 months or more with fluctuations before the start of the trial. The psychotic symptoms consisted of pure visual hallucinations (n = 2) and delirium (n = 10). The presence of delirium was based on DSM-III-R criteria for delirium. A history of dementia prior to the onset of psychosis was sought in all patients. Dementia was diagnosed based on DSM-III-R criteria.

Mianserin (Tetramide, Nippon Organon K. K.) was administered in the evening, starting with an oral dose of 20 mg/day, and was titrated over 4 weeks based on the severity of symptoms. That dose was maintained for another 4 weeks. All of the antiparkinsonian drugs were maintained from 4 weeks before and through the trial. Patients were withdrawn from the study if their psychotic manifestations increased above the baseline state. All subjects and their families provided their informed consent for their participation in this study.

We evaluated the effects of mianserin on psychosis by using a brief symptom-rating scale that consisted of eight items. Seven items were taken from the Gottfries, Bråne and Steen (GBS) scale (Gottfries et al. 1982) and the expanded brief psychiatric rating scale (BPRS; Lukoff et al. 1986), with slight modifications. The choice to use these items was based on the diagnostic critiera for delirium in DSM-III-R. The rating scale and items appear in Table 1.

K. Ikeguchi (✉)
Department of Neurology, Jichi Medical School,
Minamikawachi Tochigiken 329-04, Japan

A. Kuroda
Department of Psychiatry,
Tokyo Metropolitan Matsuzawa Hospital, Kamikitazawa 2-1-1,
Setagaya, Tokyo 156, Japan

Table 1 Scale for evaluating psychotic symptoms (range 0 – 6). 0 no significant disruption in sleep at night; 1 very mild sleep continuity disturbance; 2 mild sleep continuity disturbance with 6 h or more of total sleep time (TST); 3 moderate sleep continuity disturbance with less than 6 h of TST; 4 moderately severe sleep continuity disturbance and less than 4 h of TST; 5 severe sleep continuity disturbance; 6 inability to sleep at night

Distractibility[a]
Conceptual disorganization[b]
Impaired wakefulness[a]
Hallucinations[b]
Sleep disturbance
Motor hyperactivity[b]
Disorientation[b]
Impaired recent memory[a]

NOTE: All symptoms fulfill entire range (0 – 6)
[a] From the GBS scale (Gottfries et al. 1982; see text)
[b] From the expanded BPRS (Lukoff et al. 1986; see text)

Our modifications were as follows: Items adapted from the expanded BPRS were rated on a 7-point scale from 0 (not present) to 6 (extremely severe); the time frame was the past 1 week; and the rating reflected mainly the peak period.

Parkinsonian disability was assessed using the Hoehn and Yahr scale (Hoehn and Yahr 1967) and the motor examination of the United Parkinson's Disease Rating Scale (UPDRS; Fahn et al. 1987). Marked improvement in psychotic symptoms was defined as a 15-point or greater decrease in total score in delirious patients, and as a 3-point or greater decrease in patients with pure hallucinations. Moderate improvement was defined as a 10- to 14-point decrease in delirious patients and a 2-point decrease in pure hallucinations. Mild improvement was defined as a 5- to 9-point decrease in delirious patients and a 1-point decrease in pure hallucinations. A decrease of less than 5 points was considered insignificant in delirious patients.

Data are reported as mean ± standard deviation. Scores before and after administration of mianserin were analyzed using paired *t*-test to determine any significant differences. A level of $P < 0.05$ was accepted as statistically significant.

Results

All of the patients completed the trial. Table 2 shows the patients' clinical characteristics. All showed a moderate disability of stage III to IV on the Hoehn and Yahr scale. Their mean durationof PD was 6.9 years. A total of 10 patients were diagnosed as having delirium and 2 patients had pure visual hallucinations. Five patients had dementia. Laboratory and neurodiagnostic investigations of these patients yielded all normal results.

The patients were treated with mianserin for 8 weeks in a mean daily maintenance dose 36.7 mg (range 20–60 mg). The drug was well tolerated and there were no serious side effects during the trial. The elimination or marked improvement of psychotic symptoms was noted in 8 patients; symptoms moderately improved in 2 patients and there was no improvement in 2 patients. The 10 patients for whom mianserin was effective were followed for another 2–12 months. Only 1 patient experienced a relapse of psychotic symptoms during that period. After the intermittent withdrawal of mianserin, the symptoms of delirium recurred within 3 days. Reinstitution of mianserin restored the previously favorable response.

The average total score for delirium decreased significantly within 7 days instituting mianserin ($P < 0.01$). The score decreased gradually from 22.0 to 5.3 in 8 weeks. Figure 1 shows the average score of each rating-scale item. The score of the hallucinatory item decreased significantly within 1 week ($P < 0.01$), and gradually decreased from 3.7 to 1.1 in 8 weeks. Scores for the other symptoms also decreased significantly within 1 week ($P < 0.05$). None of the patients exhibited psychomotor hypoactivity during the study.

The parkinsonism improved slightly in 8 of the 12 patients and was unchanged in 4. The average scores of the motor exam of UPDRS decreased from 38.5 ± 6.2 to 37.4 ± 6.6, a slight, but significant ($P < 0.01$), improvement.

Discussion

We found that mianserin, a 5-HT_2 receptor antagonist, effectively ameliorated drug-induced psychiatric symptoms in the patients with PD without exacerbating their motor disability. These findings suggest that the serotonin system at 5-HT_2 receptors may participate in the

Table 2 Clinical characteristics and treatment of patients with psychosis. AC anticholinergic drugs; AMA amantadine; BR bromocriptine; DOPA levodopa; DOPA/CD levodopa/carbidopa

Parkinsonism				Dementia	Antiparkinsonian drugs	Psychosis	Mianserin (mg/day)
Age (years)	Gender	Stage[a]	Duration (years)				
69	F	4	6	Mild	AMA, BR, DOPA/CD	Hallucinations	40
75	F	4	11	Mild	AMA, BR, DOPA/CD	Hallucinations	30
65	F	3	7	None	BR, DOPA/CD	Delirium	30
66	F	4	8	Mild	AC, AMA, BR, DOPA/CD	Delirium	40
67	F	3	5	None	AC, AMA, DOPA/CD	Delirium	30
69	M	4	6	None	AC, BR, DOPA	Delirium	20
72	M	3	6	None	BR, AC, AM, DOPA	Delirium	30
73	F	4	4	None	AC, AMA	Delirium	60
73	M	4	8	None	AC, BR	Delirium	60
74	M	3	5	Moderate	AC, BR	Delirium	60
76	M	4	8	Mild	DOPA/CD	Delirium	20
82	F	4	9	Moderate	DOPA/CD	Delirium	20

[a] From Hoehn and Yahr (1967)

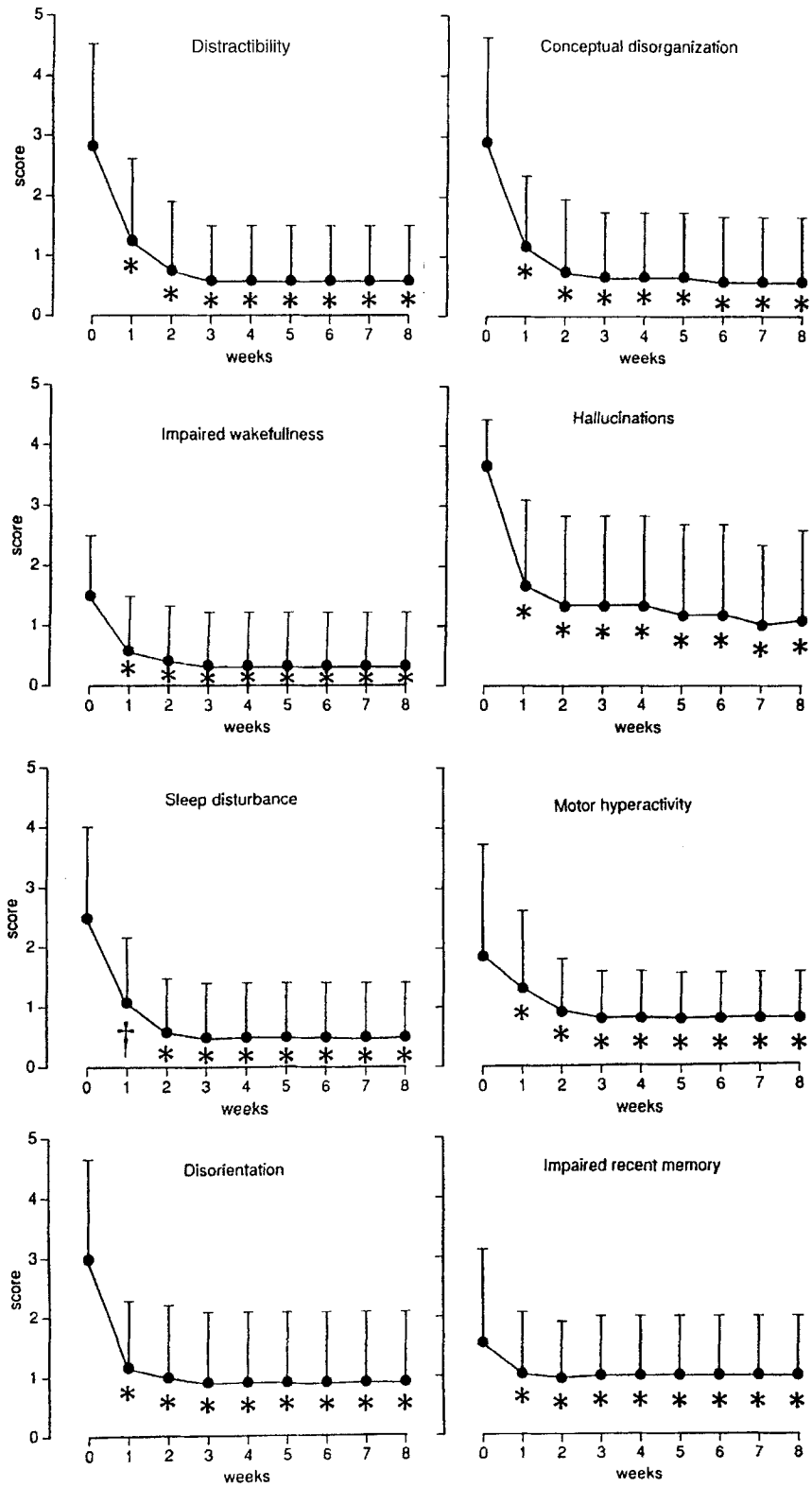

Fig. 1 Average score of each item of the brief rating scale. Data are expressed as mean ± standard deviation. Significance of differences between score before and after mianserin medication was analyzed by paired *t*-test (*dagger* $P < 0.05$; *asterisks* $P < 0.01$)

development of drug-induced psychosis in PD, and that antagonism of 5-HT_2 receptors may be important in treating PD.

The rapid disappearance of the psychiatric symptoms that had continued for more than 3 months before the start of the mianserin adminstration may represent a pharmacological effect of mianserin treatment. Mianserin's ameliorating effects on hallucinations in PD patients with drug-induced psychosis may be attributable to serotonergic antagonism at 5-HT_2 receptors, because it has been demonstrated that most hallucinogens are serotonergic agonists at 5-HT_2 receptors (Glennon et al. 1984). Also, effects of

hallucinogens in animal studies were attenuated by 5-HT_2 antagonists (Glennon et al. 1983).

Serotonergic antagonism at 5-HT_2 receptors may also account for the improvement in sleep disturbance in drug-induced psychosis in PD by mianserin, because ritanserin, another 5-HT_2 antagonist, increased the slow-wave sleep in both volunteers (Idzikowsky et al. 1986; Declerck et al. 1987) and in dysthymic patients (Paiva et al. 1988). Ritanserin was also reported to reduce negative symptoms of schizophrenic patients (Duinkerke et al. 1993). Lessening of the other symptoms may have been secondary to the effects of 5-HT_2 receptor antagonism on hallucinations and sleep disturbance.

Mianserin is a relatively selective antagonist at 5-HT_2 receptors (Peroutka 1987). It is also an atypical antidepressant that lacks activity on the monoamine reuptake mechanism and cholinergic receptors, and it blocks the α_2 adrenoreceptors (Brogden et al. 1978). Because mianserin's effects on drug-induced psychosis were observed within 7 days of treatment, they cannot be attributed to mianserin's antidepressant action, which requires several weeks for clinical effectiveness (Baldessarini 1990). The rapidity with which improvement became apparent suggests that it was attributable to mianserin's 5-HT_2 receptor antagonism.

Our findings were compatible with those of a study reporting that serotonin and 5-hydroxyindoleacetic acid (5-HIAA) levels were significantly higher in the extrapyramidal areas of PD patient's brain with vs without psychosis (Birkmayer 1978). In contrast to our results, the administration of a serotonin precursor in previous uncontrolled studies reportedly alleviated drug-induced psychosis in PD patients (Lehmann 1973; Gehlen and Müller 1974), and a serotonin deficiency mechanism of the psychosis was suggested. However controlled study failed to demonstrate any improvement (Beasley et al. 1980).

Drug-induced psychosis in PD has also been effectively treated with clozapine (Scholz and Dichgans 1985). Clozapine exhibits potent dopamine D_4 (Van Tol et al. 1991), D_1, 5-HT_2, and muscarinic receptor antagonistic activities, but a weak D_2 receptor antagonistic activity (Fitton and Heel 1990). Although clozapine's activities on multiple receptors make it difficult to clarify which receptor is primarily involved in its mechanism of action, our clinical results indicate that its effects may be attributable to antagonism at 5-HT_2 receptors. The usefulness of clozapine was limited by the following: delirium, which may be a manifestation of its central anticholinergic toxicity (Schuster et al. 1977), and a tendency to increase parkinsonism (Wolters et al. 1990). These side effects less frequently or never occurred with mianserin (Blackwell 1984; Brogden et al. 1978). Mianserin is superior to clozapine in this regard. In patients with drug-induced psychosis who did not respond to mianserin, nonserotonergic systems, such as dopaminergic (Celesia and Barr 1970) and cholinergic (De Smet et al. 1982) systems, might play a major role in symptom development.

We used DSM-III-R criteria for diagnosing delirium and for excluding other mental disorders in patients with PD. In that reference source, the clouding of consciousness that was previously required in DSM-III was redefined as a reduced level of consciousness, and became one of six criteria, two or more of which had to be present for a diagnosis of delirium. Disorientation and memory impairment were also among these six criteria, although they were no longer absolutely required. Consequently, the criteria for delirium in DSM-III-R were met by the majority of patients who were previously diagnosed with drug-induced psychosis in PD.

We presented a symptom rating scale that included characteristic symptoms of delirium based on DSM-III-R. It quantitated the severity of delirium, and could be used to monitor the response to treatment. The Delirium Rating Scale (DRS; Trzepacz et al. 1988) also included characteristic symptoms of delirium, but it emphasized the ability to identify delirium, rather than to quantitate severity with regard to such items as temporal onset of symptoms, hallucination type, and physical disorder. We therefore did not use the DRS to evaluate drug effects in our study.

Reduction of parkinsonism by the administration of mianserin may occur via 5-HT_2 antagonism. Several findings support this assumption:

1. Ritanserin, a selective 5-HT_2 antagonist, reportedly reduces haloperidol-induced parkinsonism (Bersani et al. 1986; Gelder et al. 1986). In contrast to our results, Korsgaard and Friis (1986) reported that mianserin failed to improve neuroleptic-induced parkinsonism. The discrepancies between their results and ours may be due to the fact that in their study, a portion of 5-HT_2 receptors may have been already occupied by neuroleptics, because most of these neuroleptics were 5-HT_2 antagonists as well as D_2 antagonists (Meltzer and Nash 1991). In our study hyperactivity or preservation of the serotonin system is suggested by the presence of psychosis.
2. Fluoxetine, an antidepressant with strong and selective serotonin uptake inhibitory action and devoid of anticholinergic activity (Schmidt et al. 1988), reportedly increases motor disability in drug-induced parkinsonism (Tate 1989; Bourchard et al. 1989) and in PD (Steur et al. 1993).
3. The deterioration of parkinsonism after the administration of the serotonin precursor 5-hydroxytryptophan (5-HTP) has been reported (Chase 1970; Chase et al. 1972).

An alternative mechanism of mianserin action is via antagonism of the presynaptic α_2 adrenoreceptor, which potentiates norepinephrine transmission and ameliorates parkinsonism in a manner similar to that of L-threo-3,4-dihydroxyphenylserine (L-threo-DOPS), a norepinephrine precursor (Narabayashi et al. 1981).

In conclusion, 5-HT_2 receptor antagonism may be important in treating patients with antiparkinsonian drug-induced psychosis in PD, and may also slightly ameliorate the parkinsonism.

References

American Psychiatric Association (1980) Diagnostic and statistical manual of mental disorders (DSM-III). American Psychiatric Association; Washington, DC

American Psychiatric Association (1987) Diagnostic and statistical manual of mental disorders (DSM-III-R), 3rd edn, revised. American Psychiatric Association, Washington, DC

Baldessarini RJ (1990) Drugs and the treatment of psychiatric disorders. In: Gilman AG, Rall TW, Nies AS, Taylor P (eds) Goodman and Gilman's the pharmacological basis of therapeutics. Pergamon Press, New York, pp 383–435

Beasley BL, Nutt JG, Davenport RW, Chase TN (1980) Treatment with tryptophan of levodopa-associated psychiatric disturbances. Arch Neurol 37:155–156

Bersani G, Grispini A, Marini S, Pasini A, Valducci M, Ciani N (1986) Neuroleptic-induced extrapyramidal side effects: clinical perspectives with ritanserin (R 55667), a new selective 5-HT_2 receptor blocking agent. Curr Ther Res 40:492–499

Birkmayer W (1978) Toxic delirium after L-dopa medication. J Neural Transm (Suppl) 14:163–166

Blackwell B (1984) Antidepressant drugs. In: Dukes MNG (ed) Meyler's side effects of drugs, 10th edn. Excerpta Medica, Amsterdam, pp 24–61

Bouchard RH, Pourchur E, Vincent P (1989) Fluoxetine and extrapyramidal side effects. Am J Psychiatry 146:1352–1353

Brogden RN, Heel RC, Speight TM, Avery GS (1978) Mianserin: a review of its pharmacological properties and therapeutic efficacy in depressive illness. Drugs 16:273–301

Celesia GG, Barr AN (1970) Psychosis and other psychiatric manifestations of levodopa therapy. Arch Neurol 23:193–200

Chase TN (1970) 5-Hydroxytryptophan in parkinsonism. Lancet 2:1029–1030

Chase TN, Ng LKY, Watanabe AM (1972) Parkinson's disease. Modification by 5-hydroxytryptophan. Neurology 22:479–484

Declerck AC, Wauquier A, Van Der Ham-Veltman, Gelders Y (1987) Increase in slow-wave sleep in humans with the serotonin-S_2 antagonist ritanserin. Curr Ther Res 41:427–432

De Smet Y, Ruberg M, Serdaru M, Dubois B, Lhermitte F, Agid Y (1982) Confusion, dementia and anticholinergics in Parkinson's disease. J Neurol Neurosurg Psychiatry 45:1161–1164

Duinkerke SJ, Botter PA, Jansen AAI, Van Dongen PAM, Van Haaften AJ, Boom AJ, Van Laarhoven JH, Busard HLSM (1993) Ritanserin, a selective 5-HT2/1C antagonist, and negative symptoms in schizophrenia. A placebo-controlled double-blind trial. Br J Psychiatry 163:451–455

Fahn S, Elton RL, UPDRS Development Committee (1987) United Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M (eds) Recent developments in Parkinson's disease. McMillian Health Information, Florham Park, New York, pp 153–163

Fitton A, Heel RC (1990) Clozapine: a review of its pharmacological properties and therapeutic use in schizophrenia. Drugs 40:722–747

Gehlen W, Müller J (1974) Zur Therapie der Dopa-Psychosen mit L-Tryptophan. Dtsch Med Wochenschr 99:457–463

Gelders Y, YandenBusshe G, Reyntjens A, Janssen P (1986) Serotonin-S2 receptor blockers in treatment of chronic schizophrenia. Clin Neuropharmacol 9:325–327

Glenonn RA, Young R, Rosecrans JA (1983) Antagonism of the effects of the hallucinogen DOM and the purported 5-HT agonist quipazine by 5-HT_2 antagonists. Eur J Pharmacol 91:189–196

Glennon RA, Titeler M, McKenney JD (1984) Evidence for 5-HT_2 involvement in the mechanism of action of hallucinogenic agents. Life Sci 35:2505–2511

Gottfries CG, Bråne G, Steen G (1982) A new rating scale for dementia syndromes. Gerontology 28 (Suppl 2):20–31

Hoehn MM, Yahr MD (1967) Parkinsonism: onset, progression and mortality. Neurology 17:427–442

Idzikowski C, Mills FJ, Glennard R (1986) 5-Hydroxytryptamine-2 antagonist increases human slow-wave sleep. Brain Res 378:146–148

Korsgaard S, Friis T (1986) Effects of mianserin in neuroleptic-induced parkinsonism. Psychopharmacology 88:101–111

Lehmann J (1973) Tryptophan malabsorption in levodopa-treated parkinsonian patients. Effects of tryptophan on mental disturbances. Acta Med Scand 194:181–189

Lukoff D, Neuchterlein KH, Ventura J (1986) Manual for expanded brief psychiatric rating scale (BPRS). Schizophr Bull 12:594–602

Meltzer HY, Nash JF (1991) Effects of antipsychotic drugs on serotonin receptors. Pharmacol Rev 43:587–604

Narabayashi H, Kondo T, Hayashi A, Suzuki T, Nagatsu T (1981) L-threo-3,4-dihydroxyphenylserine treatment for akinesia and freezing of parkinsonism. Proc Jpn Acad 57(B):351–354

Paiva T, Arriaga F, Wauquier A (1988) Effects of ritanserin on sleep disturbances of dysthymic patients. Psychopharmacology 96:395–399

Peroutka SJ (1987) Serotonin receptors. In: Meltzer HY (ed) Psychopharmacology: the third generation of progress. Raven Press, New York, pp 303–311

Schmidt MJ, Fuller RW, Wong DT (1988) Fluoxetine, a highly selective serotonin reuptake inhibitor: a review of preclinical studies. Br J Psychiatry 153 (Suppl 3):40–46

Scholz E, Dichgans J (1985) Treatment of drug-induced exogenous psychosis in parkinsonism with clozapine and fluperlapine. Eur Arch Psychiatry Neurol Sci 235:60–64

Schuster P, Gabriel E, Kufferle B, Stobl G, Karobath M (1977) Reversal by physostigmine of clozapine-induced delirium. Clin Toxicol 10:437–441

Steur EN (1993) Increase of Parkinson disability after fluoxetine medication. Neurology 43:211–213

Tate JL (1989) Extrapyramidal symptoms in a patient taking haloperiodol and fluoxetine. Am J Psychiatry 146:399–400

Trepacz PT, Baker RW, Greenhouse J (1988) A symptom rating scale for delirium. Psychiatry Res 23:89–97

Van Tol HH, Bunzow JR, Guan HC, Sunahara RK, Seeman P, Niznik HB, Civelli O (1991) Cloning of the gene for a human dopamine D4 receptor with high affinity for the antipsychotic clozapine. Nature 350:610–614

Wolters EC, Hurwitz TA, Mak E, Teal P, Peppard FR, Remick R, Calne S, Calne DB (1990) Clozapine in the treatment of parkinsonian patients with dopaminergic psychosis. Neurology 40:832–834