Clozapine Treatment for Neuroleptic-Induced Tardive Dyskinesia, Parkinsonism, and Chronic Akathisia in Schizophrenic Patients

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Background: Previous studies on the use of clozapine in neuroleptic-resistant chronic schizophrenic patients have demonstrated positive effects on tardive dyskinesia but were less conclusive about chronic akathisia and parkinsonism. The aim of the present study was to investigate the short-term (18 weeks) efficacy of clozapine in neuroleptic-resistant chronic schizophrenic patients with coexisting tardive dyskinesia, chronic akathisia, and parkinsonism.

Method: Twenty chronic, neuroleptic-resistant schizophrenic patients with coexisting tardive dyskinesia, parkinsonism, and chronic akathisia were treated with clozapine. Assessment of tardive dyskinesia, parkinsonism, and chronic akathisia was made once weekly for 18 weeks with the Abnormal Involuntary Movement Scale (AIMS), Simpson-Angus Rating Scale for Extrapyramidal Side Effects, and Barnes Rating Scale for Drug-Induced Akathisia (BAS).

Results: At the end of 18 weeks of clozapine treatment, improvement rates were 74% for tardive dyskinesia, 69% for parkinsonism, and 78% for chronic akathisia. A statistically significant reduction in the scores on the AIMS and Simpson-Angus Scale was achieved at Week 5 and on the BAS at Week 6 ($p < .0001$).

Conclusion: Relatively low doses of clozapine are effective for the treatment of neuroleptic-induced extrapyramidal syndromes in neuroleptic-resistant chronic schizophrenic patients. The relief of tardive dyskinesia, parkinsonism, and chronic akathisia in this group of patients occurs more rapidly than the reduction in psychotic symptoms. Disturbing, long-term extrapyramidal syndromes in chronic schizophrenic patients should be considered an indication for clozapine treatment.

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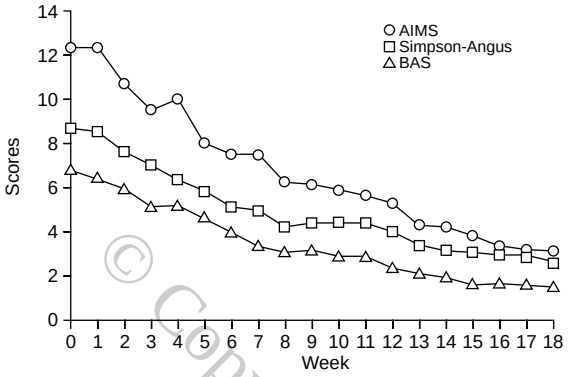
Chronic akathisia, parkinsonism, and tardive dyskinesia (TD) are the classic extrapyramidal syndromes (EPS) seen during conventional long-term neuroleptic therapy in up to 75% of patients.[1–3] These side effects are distressing to patients and limit their possibilities for social integration and rehabilitation.[2] All entail a risk of becoming irreversible.[2]

All traditional neuroleptics may induce EPS with different individual rates of incidence[1] depending on their ability to occupy D_2 dopamine receptors in the basal ganglia.[4] Tardive dyskinesia, chronic akathisia, and parkinsonism may occur concurrently,[5] although not all studies have reported this association.[1] The prevalence of TD, chronic akathisia, and parkinsonism in chronic schizophrenic patients has been reported to be as high as 50%, 40%, and 65%, respectively.[2,6–8]

Unlike conventional neuroleptic agents, clozapine is associated with only a low incidence of EPS (6% for tremor, 6% for akathisia, and 3% for rigidity) and has even been considered useful for the treatment of chronic neuroleptic-induced EPS.[9–11] Previous studies have shown that about half of all cases of neuroleptic-induced tardive dyskinesia are alleviated with clozapine treatment.[3] However, the short-term influence of clozapine on neuroleptic-induced akathisia and parkinsonism has not been extensively investigated.

The purpose of this study was to determine the efficacy of short-term (18 weeks) clozapine treatment in neuroleptic-resistant chronic schizophrenic patients with coexisting TD, chronic akathisia, and parkinsonism.

Figure 1. Mean Weekly Scores for the AIMS, Simpson-Angus, and BAS During the 18 Weeks of Clozapine Treatment*



*Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Rating Scale for Drug-Induced Akathisia, Simpson-Angus = Simpson-Angus Rating Scale for Extrapyramidal Side Effects.

PATIENTS AND METHOD

Twenty neuroleptic-resistant chronic schizophrenic patients (10 men and 10 women) with EPS were included in the study. Mean ± SD prestudy patient age was 43.1 ± 7.1 years, mean duration of disease was 17.0 ± 8.7 years, and mean number of hospitalizations was 4.5 ± 3.6. The mean ± SD dose of neuroleptics in chlorpromazine equivalents was 337 ± 107 mg/day. The diagnosis of chronic schizophrenia was made after a structured interview, according to the guidelines of the Structured Clinical Interview for Axis I DSM-IV Disorders-Patient Version (SCID-P),[12] as based on the DSM-IV criteria. Neuroleptic resistance was defined as failure to respond to three neuroleptic agents of different classes during 6 weeks of treatment for each and no episodes of complete symptomatic remission during the last 5 years.[13] All patients were in good physical condition, without either chronic or current physical or neurologic problems, history of alcohol and/or drug abuse, or abnormalities on routine laboratory tests. All gave their informed consent after the procedure and possible side effects were fully explained to them.

At baseline, tardive dyskinesia was diagnosed according to the Schooler and Kane criteria,[14] parkinsonism was measured according to the Simpson-Angus Rating Scale for Extrapyramidal Side Effects (Simpson-Angus),[15] and akathisia according to the Barnes Rating Scale for Drug-Induced Akathisia (BAS).[16] All 20 patients met the DSM-IV research criteria for the three disorders.

A total of 65 neuroleptic-resistant chronic shizophrenic patients were screened to find the 20 who showed evidence of TD, parkinsonism, and chronic akathisia.

Patients began clozapine treatment after a 2-week washout period from previous psychotropic medication. Clozapine dose was gradually increased according to clinical response, which was monitored from baseline to Week 18 of treatment with the Positive and Negative Syndrome Scale (PANSS),[17] Hamilton Rating Scale for Depression (HAM-D),[18] and Hamilton Rating Scale for Anxiety (HAM-A).[19] Tardive dyskinesia, parkinsonism, and akathisia were assessed weekly with the Abnormal Involuntary Movement Scale (AIMS),[20] the Simpson-Angus, and the BAS, respectively.

Statistical analysis was performed using analysis of variance with repeated measures (ANOVA) and the Bonferroni post hoc test to assess the significance of weekly changes in the scores on the PANSS, HAM-D, HAM-A, AIMS, Simpson-Angus, and BAS. The Pearson correlation test was performed to assess the correlation between psychometric symptoms and EPS. All results are expressed as mean ± SD values.

RESULTS

Clozapine dose was increased from 46.2 ± 21.1 mg/day in the first week of treatment to 208.7 ± 176.6 mg/day in the 18th week. There was no significant change in mean clozapine dose from Week 10 to 18 of treatment.

The clinical response to clozapine and the effect of the treatment on symptoms of tardive dyskinesia, parkinsonism, and akathisia are summarized in Table 1. During the 18 weeks of clozapine treatment, there was gradual and continuous improvement in all three syndromes (tardive dyskinesia, parkinsonism, and chronic akathisia) (Figure 1) (AIMS: $F = 16.7$, $p < .0001$; Simpson-Angus: $F = 15$, $p < .0001$; BAS: $F = 15.3$, $p < .0001$, by ANOVA). By Week 18, rates of improvement were 74% for tardive dyskinesia, 69% for parkinsonism, and 78% for akathisia. A statistically significant reduction ($p < .0001$) in tardive dyskinesia and parkinsonism was already achieved at Week 5 (35% and 32%, respectively), and in chronic akathisia (41%) at Week 6 (Table 1).

After 18 weeks of clozapine treatment, the total, positive, and negative PANSS scores gradually decreased. The total PANSS score had decreased by 32%. The improvement in positive symptoms was 36% and in negative symptoms, 27% (total PANSS score: $F = 15.7$, $p < .0001$; positive symptoms: $F = 12.9$, $p < .0001$; negative symptoms: $F = 12.1$, $p < .0001$, by ANOVA). The decrease in the total PANSS positive and negative scores was statistically significant ($p < .0001$) by Week 4 of clozapine treatment (Table 1).

The final improvement in the HAM-D and HAM-A was 57% and 48%, respectively (HAM-D: $F = 12.8$, $p < .0001$; HAM-A: $F = 8.5$, $p < .0001$, by ANOVA). In both scales, a significant reduction was detected at Week 5 ($p < .05$ and $p < .01$, respectively) (Table 1).

Changes on the AIMS, Simpson-Angus, and BAS were strongly correlated with all changes in the positive, negative, and total PANSS scores and the HAM-D and

Table 1. Effects of 18 Weeks of Clozapine Treatment in 20 Neuroleptic-Resistant Chronic Schizophrenic Patients (Mean ± SD)*

		Wk of Clozapine Treatment																	ANOVA-RM	
	Baseline	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	F	p
Dose of clozapine (mg/d)																					
Mean	0	46.2	91.2	13.0	140.6	164.4	169.4	183.1	190.6	190.6	203.7	208.7	213.1	200.6	203.1	204.4	210.0	208.7	208.7		
SD	0	21.1	46.8	77.1	94.0	112.3	116.7	121.4	119.0	122.0	131.4	137.9	140.8	149.0	152.9	167.6	175.9	176.6	176.6		
AIMS																					
Mean	12.3	12.3	10.7	9.5	10.1	8.0[b]	7.5	7.5	6.7	6.2	5.9	5.7	5.3	4.3	4.2	3.8	3.4	3.2	3.2[d]	16.7	< .0001
SD	10.1	10.1	9.1	8.0	9.3	6.6	6.6	6.7	5.5	5.7	6.3	5.9	5.7	5.0	5.1	4.7	4.2	3.9	3.9		
Simpson-Angus																					
Mean	8.7	8.5	7.6	7.0	6.4	5.9[b]	5.1	5.0	4.2	4.4	4.4	4.4	4.0	3.4	3.2	3.1	3.0	3.0	2.7[d]	15	< .0001
SD	5.7	5.7	5.6	4.6	3.7	3.4	3.6	3.7	3.4	3.2	3.4	3.3	3.2	3.0	2.9	2.6	2.8	2.8	2.6		
BAS																					
Mean	6.8	6.4	6.0	5.2	5.2	4.6	4.0[c]	3.4	3.1	3.2	2.9	2.9	2.4	2.1	2.0	1.6	1.7	1.6	1.5[d]	15.3	< .0001
SD	4.3	4.3	3.6	3.5	3.8	3.6	3.2	2.9	2.5	2.3	2.5	2.8	2.8	2.6	2.7	2.2	2.3	2.2	2.1		
PANSS Total																					
Mean	114.9	112.7	109.7	104.4	98.8[c]	100.1	96.5	93.3	93.3	90.5	89.5	92.1	87.7	84.4	83.4	84.4	82.9	78.9	77.9[d]	15.7	< .0001
SD	24.2	21.3	23.4	23.5	27.6	29.1	28.1	26.3	26.5	24.5	24.8	26.4	25.2	25.9	29.6	31.2	31.8	28.3	26.6		
Positive																					
Mean	23.7	22.6	21.9	20.7	15.1[c]	19.6	19.0	18.4	18.2	17.9	17.9	17.8	16.9	16.4	16.5	16.3	16.0	15.3	15.1[d]	12.9	< .0001
SD	7.0	6.5	6.3	6.4	7.1	7.4	6.9	6.7	6.3	7.0	8.1	7.3	6.4	7.3	7.9	7.7	7.4	6.4	6.2		
Negative																					
Mean	29.1	27.8	27.8	26.3	25.4[b]	26.0	25.5	24.5	24.1	23.5	23.5	24.0	23.0	22.3	22.5	22.1	21.7	21.3	21.2[d]	12.1	< .0001
SD	5.7	5.7	5.2	5.6	7.3	8.1	7.3	6.9	7.1	6.9	6.9	6.6	6.6	6.8	7.2	6.7	6.4	6.2	6.2		
HAM-D																					
Mean	22.3	20.0	19.1	19.4	18.9	16.9[a]	16.4	15.4	15.2	13.6	13.4	13.1	10.8	11.1	11.8	10.7	10.7	10.7	9.5[d]	12.8	< .0001
SD	8.9	8.0	9.6	10.5	11.3	8.4	8.8	8.2	8.4	8.0	7.5	8.4	6.9	8.2	9.6	9.4	100.0	9.8	7.7		
HAM-A																					
Mean	19.8	19.6	17.9	16.0	16.9	15.4[b]	15.2	14.4	14.1	14.2	14.1	14.0	13.9	12.9	12.3	11.2	11.3	10.5	10.2[d]	8.5	< .0001
SD	9.4	9.6	9.8	9.5	10.5	9.5	9.4	8.6	8.0	8.3	8.7	9.0	9.7	9.5	9.5	9.1	10.7	9.7	10.1		

*Abbreviations: AIMS = Abnormal Involuntary Movement Scale; ANOVA-RM = ANOVA with repeated measures; BAS = Barnes Rating Scale for Drug-Induced Akathisia; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; PANSS = Positive and Negative Syndrome Scale; Simpson-Angus = Rating Scale for Extrapyramidal Side Effects. Significance vs baseline score: [a]p < .05, [b]p < .01, [c]p < .001, [d]p < .0001.

HAM-A scores: r = .97 to .99, p < .0001, by Pearson correlation test. Moreover, changes on all the EPS scales were in strong correlation with each other (AIMS and Simpson-Angus: r = .99, p < .0001; AIMS and BAS: r = .99, p < .0001; Simpson-Angus and BAS: r = .99, p < .0001, by Pearson correlation). There was also a strong negative correlation between clozapine dose and the AIMS (r = –.91, p < .0001), Simpson-Angus (r = –.93, p < .0001), and BAS (r = –.92, p < .0001) scores, by Pearson correlation test, i.e., the higher clozapine doses (in our dose range) were associated with less extrapyramidal symptoms.

DISCUSSION

The main findings of this study on the effect of clozapine in neuroleptic-resistant chronic schizophrenic patients with EPS were (1) A significant improvement in symptoms of tardive dyskinesia (74%), chronic akathisia (78%), and parkinsonism (69%) was achieved with 18 weeks of clozapine treatment. (2) Clozapine significantly decreased the symptoms of tardive dyskinesia (35%) and parkinsonism (32%) during the first 5 weeks of treatment, and symptoms of chronic akathisia (41%) during the first 6 weeks of treatment; therefore, with clozapine therapy, the improvement in EPS was more prominent and occurred more rapidly than the reduction in psychotic positive (17.3% at 5 weeks) and negative symptoms (10.7% at 5 weeks). (3) Clozapine may be effective in relatively low doses (208.7 ± 176.6 mg/day) for the reduction of both EPS as well as psychotic symptoms. (4) The reduction in depression and anxiety symptoms in our sample of neuroleptic-resistant schizophrenic patients may indicate an antidepressant and antianxiety action of clozapine,[21–23] which may contribute to the feeling of well-being and to the relief of the subjective components of EPS caused by traditional neuroleptics.

Several open, single-blind, and double-blind studies have shown a significant improvement in tardive dyskinesia in a large proportion of patients with clozapine treatment.[10,24–28] However, the time required for this improvement is variable. In our study, considerable relief of tardive dyskinesia symptoms was already obtained at Week 5 of treatment. This finding is consistent with some previous observations,[24,27] although other studies have shown significant improvement only after long-term (> 6 months) clozapine administration.[25,26,29]

The reported clozapine dosage needed to manage tardive dyskinesia varies from ≥ 500 mg/day,[25,26,28] much higher than the average dose for neuroleptic-resistant chronic schizophrenia,[30] to 300 mg/day.[10,24] In our study, the average dose (208.7 mg/day) was much lower than that used in the United States (444 mg/day)[30] and even lower than that used in Europe (293.7 mg/day).[30] This low dosage may prevent the development of serious adverse effects such as seizures and confusion. However, it is still possible that doses somewhat higher than those used in our study may be optimal for the treatment of both psychosis and for neuroleptic-induced EPS.

Clozapine has been associated with a low incidence of acute neuroleptic-induced parkinsonism.[3,9] In some cases, parkinsonian signs such as bradykinesia were detected, but never rigidity and, rarely, tremor.[3] In clozapine-treated patients, the prevalence of such parkinsonian symptoms as tremor (3%–6%) and rigidity (0%–3%)[2,3,9,11,13,31] is significantly lower than with the traditional antipsychotic agents (10%–35% and 12%–25%, respectively),[2] but the prevalence of bradykinesia is relatively high (33%), although still significantly lower in comparison to traditional neuroleptics (45%–65%).[2] This high prevalence of bradykinesia may be explained by clozapine-induced hypotonia.[2] At high doses of clozapine, the hypotonia may be prominent, such that in some reports, the high frequency of bradykinesia observed may have been related to the use of high doses of clozapine (400 mg median daily dose).[3] Therefore, it remains unclear if bradykinesia in clozapine patients is a true parkinsonian symptom.[2,3] Our results, which are consistent with a previous observation,[13] show that a significant reduction in parkinsonism, as measured by the Simpson-Angus, may already be achieved by the first 4 to 6 weeks of clozapine treatment, and an additional gradual improvement can be expected with a continuation of clozapine administration.

The therapeutic influence of clozapine on parkinsonian symptoms has been found not only in neuroleptic-resistant chronic schizophrenic patients, but also in patients with Parkinson's disease.[32] A number of studies have shown at least a moderate improvement in resting and essential tremor and a reduction in levodopa-induced dyskinesia in Parkinson's disease patients after clozapine treatment.[33–36]

While most studies have confirmed that neuroleptic-induced parkinsonism and tardive dyskinesia are significantly less common in patients taking clozapine as compared to patients receiving traditional neuroleptics, not all are in consensus about the frequency of akathisia in these patients. Two studies have reported similar rates of mild akathisia in schizophrenic patients treated with clozapine and conventional neuroleptics,[37,38] but in a recent study, significantly lower rates of subjective and objective akathisia were found in clozapine-treated patients.[3] In the review of Gerlach and Peacock,[2] 14% of patients treated long term with clozapine had subjective akathisia and 7% had objective akathisia, in comparison to 40% and 29%, respectively, of patients treated long term with neuroleptics. Povlsen et al.,[31] in a 12-year follow-up, showed no akathisia at all in clozapine-treated patients versus 23% in patients treated with conventional neuroleptics. Our results are consistent with a recent observation[3,39] that clozapine administration to neuroleptic-resistant chronic schizophrenic patients significantly reduces the severity

and clinical expression of previously existing chronic akathisia.

Long-term EPS are a common problem in chronic schizophrenic patients with a long history of treatment with traditional neuroleptics. Many kinds of pharmacologic agents have been proposed to treat tardive EPS, including cholinergic, GABAergic, and dopaminergic agents, as well as peptides, β-blockers, and lithium, but these have usually shown only a partial effect.[2] Clozapine, in contrast to the classic neuroleptics, has a low affinity for and low occupancy of the striatal dopamine-D_2 receptors.[33,40] Therefore, it is possible that long-term clozapine treatment may affect the basal ganglia motor system at a magnitude similar to that of a period free of traditional neuroleptics.[10] Previous observations have shown that EPS can be reduced after a long-term period free of classic neuroleptics.[10,41] This mechanism may be responsible for the efficacy of long-term clozapine treatment for neuroleptic-induced EPS. Nevertheless, our data and those of others[13,25] have revealed a significant rapid reduction in EPS (in the first 4 to 6 weeks) after the initiation of clozapine treatment. It is possible that the rapid efficacy of clozapine in EPS patients is related to its strong central antiserotonergic and anticholinergic activity.[31,42]

We conclude that disturbing, long-term extrapyramidal symptoms in neuroleptic-treated chronic schizophrenic patients should be considered an indication for clozapine treatment.

Drug names: clozapine (Clozaril), levodopa (Larodopa).

REFERENCES

1. McCreadie RG, Robertson LG, Wiles DH. The Nithsdale schizophrenia surveys, IX: akathisia, parkinsonism, tardive dyskinesia and plasma neuroleptic levels. Br J Psychiatry 1992;161:793–799
2. Gerlach J, Peacock L. Intolerance to neuroleptic drugs: the art of avoiding extrapyramidal syndromes. European Psychiatry 1995;10(suppl 1):27–31
3. Gerlach J, Peacock L. Motor and mental side effects of clozapine. J Clin Psychiatry 1994;55(9, suppl B):107–109
4. Farde L, Nordström AL, Wiesel F-A, et al. Positron emission tomographic analysis of central D_1 and D_2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine: relation to extrapyramidal side effects. Arch Gen Psychiatry 1992;49:538–544
5. Barnes TRE, Braude WM. Akathisia variants and tardive dyskinesia. Arch Gen Psychiatry 1985;42:874–878
6. Sachdev P. The epidemiology of drug-induced akathisia, II: chronic, tardive, and withdrawal akathisias. Schizophr Bull 1995;21:451–461
7. Woerner MG, Kane JM, Liberman JA. The prevalence of tardive dyskinesia. J Clin Psychopharmacol 1991;11:34–42
8. Youssef HA, Waddington JL. Morbidity and mortality in tardive dyskinesia: associations in chronic schizophrenia. Acta Psychiatr Scand 1987;75: 74–77
9. Safferman A, Lieberman JA, Kane JM, et al. Update on the clinical efficacy and side effects of clozapine. Schizophr Bull 1991;17:247–261
10. Tamminga CA, Thaker GK, Moran M, et al. Clozapine in tardive dyskinesia: observations from human and animal model studies. J Clin Psychiatry 1994;55(9, suppl B):102–106
11. Casey DE. Clozapine: neuroleptic-induced EPS and tardive dyskinesia. Psychopharmacology (Berl) 1989;99:47–53
12. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for Axis I DMS-IV Disorders, Patient Version (SCID-I/P, version 2.0). New York, NY: Biometric Research Department, New York State Psychiatric Institute; 1994
13. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988;45:789–796
14. Schooler NR, Kane JM. Research diagnoses for tardive dyskinesia [letter]. Arch Gen Psychiatry 1982;39:486–487
15. Simpson G, Angus JWS. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970;45(suppl 212):11–19
16. Barnes TRE. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672–676
17. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276
18. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
19. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55
20. Rey JM, Hunt GE, Johnson GFS. Assessment of tardive dyskinesia in psychiatric outpatients using a standardized rating scale. Aust N Z J Psychiatry 1981;15:33–37
21. Nader D, Leppig M, Grohman R, et al. Efficacy and adverse effects of clozapine in the treatment of schizophrenia and tardive dyskinesia: a retrospective study of 387 patients. Psychopharmacology (Berl) 1989; 99(suppl):S73–S76
22. Parsa M, Ramirez LF, Loula EC, et al. Effect of clozapine on psychotic depression and parkinsonism. J Clin Psychopharmacol 1991;11:330–331
23. Meltzer HJ, Okayli G. Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. Am J Psychiatry 1995;152:183–190
24. Small JG, Milstein V, Marhenke JD, et al. Treatment outcome with clozapine in tardive dyskinesia, neuroleptic sensitivity, and treatment-resistant psychosis. J Clin Psychiatry 1987;48:263–267
25. Lieberman JA, Johns CA, Cooper T, et al. Clozapine pharmacology and tardive dyskinesia. Psychopharmacology (Berl) 1989;99:54–59
26. Lieberman JA, Saltz BL, Johns CA, et al. The effects of clozapine on tardive dyskinesia. Br J Psychiatry 1991;158:503–510
27. Littrell K, Magill AM. The effect of clozapine on preexisting tardive dyskinesia. J Psychosoc Nurs 1993;31:14–18
28. Simpson G, Lee JM, Shrivastava RK. Clozapine in tardive dyskinesia. Psychopharmacology (Berl) 1978;56:75–80
29. Lamberty JS, Bellnier R. Clozapine and tardive dyskinesia. J Nerv Ment Dis 1993;181:137–138
30. Fleischhacker WW, Hummer M, Kunz M, et al. Clozapine dose in the United States and Europe: implication for therapeutic and adverse effects. J Clin Psychiatry 1994;55(9, suppl B):78–81
31. Povlsen UJ, Noring U, Fog R. Tolerability and therapeutic effect of clozapine. Acta Psychiatr Scand 1985;71:176–185
32. Safferman AZ, Kane JM, Aronowitz JS, et al. The use of clozapine in neurologic disorders. J Clin Psychiatry 1994;55(9, suppl B):98–101
33. Pakkenberg H, Pakkenberg B. Clozapine in the treatment of tremor. Acta Neurol Scand 1986;73:295–297
34. Friedman JH, Lannen MC. Clozapine-responsive tremor in Parkinson's disease. Mov Disord 1990;5:225–229
35. Fischer PA, Bass H, Hefner R. Treatment of parkinsonian tremor with clozapine. J Neural Transm 1990;2:233–238
36. Bennett JP, Landow ER, Schuch LA. Suppression of dyskinesia in advanced Parkinson's disease. Neurology 1993;43:1551–1555
37. Claghorn J, Honigfeld G, Abuzzahab FS, et al. The risk and benefits of clozapine versus chlorpromazine. J Clin Psychopharmacol 1987;7: 377–384
38. Cohen BM, Keck PE, Satlin A, et al. Prevalence and severity of akathisia in patients on clozapine. Biol Psychiatry 1991;29:1215–1219
39. Levin H, Chengappa KNR, Kambhampati RK, et al. Should chronic treatment-refractory akathisia be an indication for the use of clozapine in schizophrenic patients? J Clin Psychiatry 1992;53:248–251
40. Seeman P, Guan H-C, Van Tol H, et al. Low density of dopamine D_4 receptors in Parkinson's disease, schizophrenia, and control brain striata. Synapse 1993;14:247–253
41. Jeste DV, Wyatt RJ. In search of treatment for tardive dyskinesia: review of the literature. Schizophr Bull 1979;5:251–292
42. Bolden C, Cusack B, Richelson E. Clozapine is a potent and selective muscarinic antagonist at the five cloned human muscarinic acetylcholine receptors expressed in CHO-K1 cells. Eur J Pharmacol 1991;192:205–206