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Review

Clozapine and tardive movement disorders: A review

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ABSTRACT

Background: Tardive syndromes (TS) arise from long term exposure to dopamine receptor blocking agents. Clozapine has been considered to have low risk of causing new onset TS and is considered as a treatment option in patients with TS.
Aim: This review evaluates the usefulness of clozapine in patients with TS and occasional reports of clozapine causing TS.
Methodology: Electronic searches were carried out using the search engines of PUBMED, Science direct and Google Scholar databases. All reports describing use of clozapine in management of TS, monitoring of TS while on clozapine and onset of TS after initiation of clozapine were identified.
Results: Fifteen trials and 28 case series/case reports describe the use of clozapine in TS. Most of these reports show that clozapine is useful in patients with TS, in the dose range of 200–300 mg/day and the beneficial effect is seen within 4–12 weeks of initiation. One case series and two case reports described clozapine withdrawal emergent dyskinesias suggesting a masking role of clozapine. One trial, three case series and two case reports describe beneficial effects of clozapine on long standing neurological syndromes. There is relatively less literature (2 trials and 15 case series/reports) describing the emergence of TS with clozapine.
Conclusion: Evidence of beneficial effects of clozapine in TS is greater than its role in causation/worsening of TS. Hence, clozapine should be considered in symptomatic patients who develop TS while receiving other antipsychotics. Further research on mechanism of TS and clozapine effect on TS is required.

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1. Introduction

The introduction of chlorpromazine in 1950s, followed by other antipsychotics ushered an era of optimism about the management of patients with psychotic disorders. However, the optimism was rather short lived, as by 1957 reports of extrapyramidal side effects and movement disorders associated with neuroleptics started emerging (Schonecker, 1957). Over the last 60 years a large number of antipsychotics have been developed, but it cannot be said with confidence that a particular antipsychotic medication is free of extrapyramidal side effects and movement disorders. Among the various movement disorders, one of the most distressing are the tardive syndromes (TS).

TS are understood as delayed onset disorders associated with use of dopamine receptor blocking agents characterised by abnormal movements and are recognised as tardive dyskinesia,

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Table 1
Use of clozapine for movement disorders in psychiatric conditions.

Name of Author	*N*	Type of movement disorder	Clozapine dose *n* mg/day	Baseline rating of movement disorders	Duration clozapine	Result	Remarks/outcome
Gerlach et al., 1974[a]	8	TD	225		3 weeks each dose		In 5/8 pts TD improved on HPL and 1 worsened on HPL. Clozapine had no definite effect on TD. 2/8 pts improved after withdrawal of clozapine.
Simpson et al., 1978[b]	12	TD	523–775	Mean AIMS – 26	18 weeks	Mean AIMS – 12	Moderate improvement while on clozapine. 5/10 symptoms on AIMS showed decrease
Cole et al., 1980	27	TD	100–300–21 pts >500–6 pts				Mild to moderate improvement. Greatest improvement among 12 pts treated >12 weeks – 2 had complete remission, 1 had marked improvement.
Gerbino et al., 1980	24	TD	650		7 pts–>4 weeks 17 pts – 1 year		All 24 patients showed at least 50% reduction on AIMS; 7 patients had achieved 100% remission, 12 patients ≥ 90%
Small et al., 1987	19	TD	<340	AIMS of 7 pts mean – 20		AIMS of 7 pts mean after 7 weeks – 4	All patients showed improvement in TD by clinical impression during first 7 weeks. Seven patients evaluated with AIMS showed a decrease in mean total scores from 20 to 4 after 7 weeks of treatment. Symptoms returned to their original severity at the end of the trial following drug withdrawal in all but one patient.
Lieberman et al., 1991	37	TD in 30, concomitant tardive dystonia in 8	500–900	Simpson dyskinesia scale (SDS) 2.7 ± 0.9 out of 5	25.7 ± 18.1 months	SDS score at 27.8 (18.2) months of follow up suggestive of 38% reduction in TD symptoms 50% or greater reduction in TD in 43% patients	Significant decrease in 12 wks after clozapine initiation. No further improvement or deterioration. Higher dose assoc with greater improvement; Maximum improvement in tardive dystonia.
Kalian et al., 1993							Atypical TD showed response to clozapine, propranolol, tetrabenazine combination
Littrell and Magill, 1993	12	TD					Drastic decrease in AIMS scores after 1 month f clozapine therapy and a steady decrease in scores throughout the 6 months of analysis
Chengappa et al., 1994	29	14 had TD prior to starting clozapine					10/14 patients showed complete improvement in TD on clozapine; In another 4 patients there was reduction in the severity of TD
Van Harten et al., 1996	7	Tardive dystonia, 5 pts had concommitant TD	408 (300–800)	Rated on AIMS, FMS	103.3 ± 51.7 weeks (max 3 years)		For tardive dystonia: 4 recovered totally, 2 improved considerably and 1 did not recover. For concomitant TD: 1 patient had a total, 2 partial remission, one had a very fluctuating course, one patient worsened. Another patient developed dyskinesia. Younger age of onset and shorter duration of dystonia – possible predictors of remission. Mean age of onset (mean 27.1 versus 31.9 years), and the mean duration of dystonia was shorter (1.9 versus 11.6 years) in responders.
Spivak et al., 1997	20	TD, parkinsonism, chronic akathisia	208.7 ± 176.6	AIMS–12.3 ± 10.1 Barnes Akathisia scale (BAS) – 6.8 ± 4.3 Simpson Angus scale (SAS) – 8.7 ± 5.7	18 weeks	Initial improvement at 5–6 weeks At week 18, AIMS–3.2 ± 3.9; 74% improvement in TD SAS–2.7 ± 2.6, 69% improvement in parkinsonism BAS–1.5 ± 2.1, 78% improvement in akathisia.	Significant difference at 5 weeks for TD – 35% improvement Parkinsonism 32% improvement At 6 weeks, Akathisia 41% improvement.