Risperidone and Olanzapine Induced Tardive dyskinesia: A Critical Review of Reported Cases

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ABSTRACT

Risperidone and olanzapine in treatment of psychiatric patients can provoke a plethora of tardive dyskinesias which pose problems for them. This clinical problem requires the urgent attention of mental health professionals. Hence a comprehensive research of Medline and related literature was undertaken from 1996 till August 2004. The published twenty two cases of risperidone (N=12) or olanzapine (N=10) induced tardive dyskinesia were critically reviewed and an attempt is being made to clarify the various issues associated with them. In these reports majority of patients were in younger age group, females and the interval until onset of tardive dyskinesia after initiation of risperidone or olanzapine was within one year. In eight reported cases of risperidone induced and three cases of olanzapine induced tardive dyskinesia, TD disappears either by stopping the drug or switching to other atypical antipsychotic drug. In seven cases of risperidone induced and three cases of olanzapine induced tardive dyskinesia, there was previous exposure to conventional antipsychotic drugs. It is concluded that induction of tardive dyskinesia by these medications is insufficiently documented in these reports but in some cases evidence is suggestive of the role of these drugs in development of tardive dyskinesia. There is no generally accepted treatment for tardive dyskinesia, thus long term studies with risperidone and olanzapine are needed in future to ascertain their tardive dyskinesia liability. Mental health professionals must remain vigilant about onset of tardive dyskinesia with these medications.

Key words: Risperidone, olanzapine, tardive dyskinesia

Introduction

The first published report on tardive dyskinesia is generally credited to Schonecker in 1957. Since then tardive dyskinesia (TD) remains an important clinical problem. These days atypical antipsychotics are widely used in day to day clinical practice. These are reported to have superior extrapyramidal side effect profile to that of conventional antipsychotics (Glazer, 2000). Furthermore it is claimed that the prevalence of tardive dyskinesia has dropped markedly with a switch from neuroleptics to atypical antipsychotics (Jeste, 2004; Friedman, 2004).

During the last decade a number of novel antipsychotics drugs in the market have been launched. These molecules have come with substantial number of studies supporting their use, reduced liability for inducing tardive dyskinesia and antidyskinetic properties. This has fascinated the young clinicians to try them in large number of patients. The appearance of atypical antipsychotics has opened new paths. Risperidone and olanzapine appear to be effective in psychotic patients, but several authors report cases of tardive dyskinesia during maintenance therapy with these drugs. They are doubtlessly promising, but the notion of risk-benefit aspects of these medications cannot be ignored (Lloraca, 2002).

These medications have not been used long enough or adequately studied for their effects on tardive dyskinesia. Rising number of case reporting of risperidone or olanzapine induced tardive dyskinesia is a matter of concern. It has been revealed that with these novel antipsychotics certain amount of complacency exists (Simpson, 2000). As tardive dyskinesia is relatively under recognized in the clinical setting (Hansen et al, 1992), possibility of lesser reporting of such cases in the literature cannot be ruled out.

Effects of olanzapine and risperidone on tardive dyskinesia are less clear. These published cases raise interest in this important clinical problem and this review was conducted to clarify the role played by risperidone or olanzapine in development of tardive dyskinesia.

Material and Methods

An extensive MEDLINE search and review of the literature from January 1996 till August 2004 was undertaken to collect the data of reported cases of tardive dyskinesia by risperidone or olanzapine. The search terms used were risperidone, olanzapine and tardive dyskinesia. Indian literature was also searched manually and total twenty two (N=22) reported cases were critically analyzed. Various parameters selected from these cases were age and sex.

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distribution of patients, clinical diagnosis, dose of the drug, interval until onset, previous exposure to the other drugs as well as co-medication and outcome of tardive dyskinesia in such patients. Twelve cases of risperidone induced tardive dyskinesia were reported (N=12) and ten cases were associated with olanzapine (N=10).

Critical review

Reported cases of risperidone induced tardive dyskinesia are presented in Table No. 1 and 2. Similarly the case reports of olanzapine and tardive dyskinesia are depicted in Table No. 3. These cases revealed that the patients were mostly in the younger age group.

The age of patients with reported cases was in the range of 16-56 years (Median age 28 years). Similar figure with olanzapine reported cases was in range of 21-71 years (median age 30 years). Females constituted the majority of cases in these reports. Regarding diagnosis schizophrenia represented a large majority of cases reported for both risperidone and Olanzapine (N=17). Interval until onset was within one year in majority of these cases. Median interval in risperidone induced cases was four months and in olanzapine reported cases, it was seven months. In some cases these patients were given risperidone or olanzapine as monotherapy and no typical antipsychotics were used. In seven cases of risperidone induced and three cases of olanzapine induced tardive dyskinesia, there was previous exposure to conventional antipsychotic drugs.

The dose of risperidone used was in the range of 2-12 mg/day while olanzapine dose was 10-30mg/day in these reports. In risperidone induced tardive dyskinesia, eight patients reported disappearance of tardive dyskinesia after either stopping risperidone or switching to other atypical antipsychotic drug or by dose reduction In three cases of risperidone induced tardive dyskinesia, olanzapine is used. In two cases of olanzapine induced tardive dyskinesia, quetiapine has been used. Even as monotherapy agents, in three cases of risperidone and five cases of olanzapine used published reports, patients have developed tardive dyskinesia. In these patients there was no previous exposure to conventional antipsychotics. In such cases, evidence is narrated which is suggestive of the role of these drugs in development of tardive dyskinesia. In some cases precise information about the required reviewed parameters was lacking and thus caused complications in interpretation of

Table 1

### RISPERIDONE AND TARDIVE DYSKINESIA-I

| Sl. No. | Author | Diagnosis (Age, Gender) | Drug | Dose (mg/day) | Interval until Onset | Medication until Onset | Co-medication | Outcome |
|---------|--------|-------------------------|------|---------------|----------------------|------------------------|--------------|---------|
| 1.      | Woerner et al (1996) | Undifferentiated schizophrenia (31 yrs., Male) | Risperidone | 6 mg | 1 year | Trifluoperazine | None | TD persisting on 6mg/day |
| 2.      | Buzan (1996) | Bipolar mood disorder (46 yrs., Female) | Risperidone | 6 mg | 4 weeks | Lithium + other neuroleptics, carbamazepine, valproic acid & levothyroxine | Lithium carbamazepine, levothyroxine, Vit.E | Resolution after discontinuation |
| 3.      | Sue Hong et al (1999) | Schizophrenia (21 yrs., Female) | Risperidone | 1 mg | 5 months | None | Trihexyphenidyl 2.5 mg/day | Minimized with change to sulpiride 100mg |
| 4.      | Jaffe and Simpson (1999) | Schizophrenia (43 yrs., Male) | Risperidone | 6 mg | 10 year | Chlorpromazine 1000 mg for 14 years | None | TD improved with change to olanzapine 15 mg |
| 5.      | Vasudevan et al (2002) | Paranoid Schizophrenia (56yr, Female) | Risperidone | 8 mg | 18 months | None | Trihexyphenidyl 2mg/day | Olanzapine 7.5 mg started but TD persists. |
| 6.      | Daniel et al (1996) | Undifferentiated Schizophrenia (18 yr., Male) | Risperidone | 2-3mg | 4 months | Thoridazine, Trifluoperazine, Fluphenazine | Fluoxetine | Risperidone & fluoxetine discontinued; TD much attenuated |
| 7.      | Silberbalker (1998) | Schizophrenia, 28 yrs, Male | Risperidone | *** | 1 year | Classic neuroleptics | None | **** |

Note: ***=information not available
the data. Thus several limitations were taken into consideration while analyzing these reported cases.

Discussion

Tardive dyskinesia remains a major clinical problem despite the introduction of atypical antipsychotics a decade ago. It is claimed that patients with tardive dyskinesia who are taking conventional antipsychotics are candidates to be switched to an atypical antipsychotic (Simpson, 2000). But number of reported cases of tardive dyskinesia with risperidone or olanzapine has doubled over last 3-4 years. Tardive dyskinesia with atypical antipsychotics has been the subject of increasing attention in the third millennium. This could be attributed to increased prescription of these drugs and for a longer period these days.

Several risk factors for tardive dyskinesia have been identified, such as advanced age and duration of illness (Kane et al, 1992). But these case reports findings have shown that tardive dyskinesia can occur at a relatively younger age with risperidone or olanzapine. Among other risk factor regarding sex, females experience a higher frequency of tardive dyskinesia. This observation is also revealed in these reported cases. The reason could be the influence of oestrogen on the occurrence of tardive dyskinesia. There may be additive effects of oestrogen and atypical antipsychotics on dopamine blockade. Even in postmenopausal women oestrogen decline may precipitate tardive dyskinesia by relieving this dopamine blockade. Thus presence of oestrogen in the young and lack of it in old age may be associated with tardive dyskinesia in females.

By critical review of twenty two cases of tardive dyskinesia associated with olanzapine or risperidone it can be commented that some patients may develop tardive dyskinesia while taking risperidone or olanzapine. The induction of tardive dyskinesia with risperidone or olanzapine raises the critical issue of the effects of other atypical antipsychotics which are used in clinical practice. Some of these have been recently introduced in the market. Tardive dyskinesia can be induced by clozapine (Kumet and Freeman, 2002), quetiapine (Ghelber and Belmaker, 1999). No such case report till recent have been reported with ziprasidone or aripiprazole. Animal models have also demonstrated that atypical antipsychotic can cause involuntary movements (Tamm ing et al, 1994).

Another important issue pertains to the fact that tardive dyskinesia is induced by one atypical antipsychotic drug and switching to other atypical antipsychotic tardive dyskinesia disappears (case number 3, 4, 10-13). In some

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| Sl. No. | Author (Age, Gender) | Diagnosis | Drug | Dose (mg/day) | Interval until Onset | Medication until onset | Co-medication | Outcome |
|---------|----------------------|-----------|------|---------------|---------------------|------------------------|---------------|---------|
| 8       | Kumar and Malone (2000) | Schizophrenia, (16 yrs, Female) | Risperidone | 6 mg | 9 months | Thioridazine, Zopiclone, Trifluoperazine | None | With retriial of risperidone and dose reduction to 2 mg, TD shows improvement |
| 9       | Dubbelman et al (1998) | Schizophrenia (Disorganized) with depression, (28 yrs.) | Risperidone | *** | *** | *** | Fluoxetine | *** |
| 10      | Suzuki et al (2002) | Schizophrenia, (40 yrs. Female) | Risperidone | 3-6mg | 2 month | None | Biperidin 3mg was added | Risperidone was stopped and olanzapine started; TD disappears. |
| 11      | Suzuki et al (2002) | Schizophrenia, (28 yrs, Female) | Risperidone | 9mg | 3 weeks | Amoxapine | Biperidin 6mg/day | Risperidone stopped. Quetiapine replacement done; TD disappears. |
| 12      | Suzuki et al (2002) | Schizophrenia, (24 yrs, Female) | Risperidone | 2mg | 2 month | Haloperidol, Chlorpromazine | Biperidin 2-4 mg | Replacement with Quetiapine; TD disappears. |

Note: ***=information not available
cases by decreasing the dose of the drug, tardive dyskinesia disappears (case number 8). These facts create problems in understanding the mechanism of the induction of tardive dyskinesia by atypical antipsychotics. Casey (2004) has also highlighted that explaining this mechanism remains a substantial challenge.

Four postulations have been proposed in explaining the association of fewer drug induced movement disorders with atypical antipsychotics as compared to conventional agents (Casey, 2004). First postulation is that atypical antipsychotic has greater activity in blocking serotonin-2A receptors than dopamine-2 (D2) receptors. Secondly, atypical antipsychotics block D2 receptors only long enough to cause an antipsychotic action, but not as long as conventional agents. Thirdly, in Tardive dyskinesia, the nigrostriatal dopamine receptor system might develop increased sensitivity to dopamine as a result of treatment with conventional agents, but this may not occur with atypical antipsychotics. The last one postulation is that there might be a genetic association in its development and the dopamine D3 allele.

The other critical issue in these reports is the fact that in seven cases of risperidone induced and three cases of olanzapine induced tardive dyskinesia there was exposure to typical antipsychotics prior to initiation of risperidone or olanzapine. As tardive dyskinesia is a long term adverse effect of antipsychotic drugs. Evolution of tardive dyskinesia

| Sl. No. | Author | Diagnosis (Age, Gender) | Drug | Dose (mg/day) | Interval until Onset | Medication until onset | Co-medication | Outcome |
|---------|--------|-------------------------|------|--------------|---------------------|-----------------------|---------------|---------|
| 13.     | Dunayevich and Strakowski (1996) | Schizophrenia (40 yr. Female) | Olanzapine | *** | 7 months | Loxapine Reserpine Haloperidol Trazonil Botulinum toxin Vitamin E | Divalproex 1250mg | Clozapine 200mg/day 50% improvement |
| 14.     | Gunal et al (1996) | Paranoid Schizophrenia (21 yrs. Male) | Olanzapine | *** | 1 year | None | None | *** |
| 15.     | Herran and Barquero (1999) | Schizophrenia (30 yrs., Female) | Olanzapine | 10mg Max. = 30mg | 2 months | Haloperidol 10mg/day | Trihexyphenidyl 6 mg/day | TD remained unchanged |
| 16.     | Herran and Barquero 1999 | Schizophrenia (65 yrs., Female) | Olanzapine | 10mg Max. = 20mg | 7 months | Fluphenazine decanoate 25mg/month | None | With clozapine treatment after stopping olanzapine showed no improvement |
| 17.     | Benazzi (2002) | Huntington disease | Olanzapine | *** | *** | *** | *** | *** |
| 18.     | Ananth and Kenan (1999) | Paranoid Schizophrenia (25 yrs. Male) | Olanzapine | 20 mg | 5 years | None | None | Persisting on 20 mg |
| 19.     | Sidana et al (2004) | Paranoid Schizophrenia (43 yrs. Male) | Olanzapine | 15 mg | 7 months | None | Tetrabenazine added | Olanzapine stopped, TD disappears |
| 20.     | Koch et al (2003) | *** (71 yrs. Female) | Olanzapine | *** | *** | None | Tiapride and Tetrabenazine | *** |
| 21.     | Bella and Piccoli (2002) | Behavioural disorder (62 yrs. Female) | Olanzapine | 10 mg | 4 month | None | None | None |
| 22.     | Snoddgrass et al (1999) | Alcohol related disorder (58 yrs., male) | Olanzapine | 5 mg | 1 month | Risperidone | None | Olanzapine stopped, showed improvement |

Note: ***=information not available
could simply be attributed to previous conventional antipsychotics. But in eight reported cases this assumption is negated as there was history of only monotherapy at onset of illness with either risperidone (N=3, case no.3, 5, 10) or olanzapine (N=5, case no.14, 18 to 21). In these three risperidone induced cases, all were females and interval of onset of TD was in the range of 2 to 18 months after initiation of risperidone. In contrast to these finding in olanzapine induced cases, three patients were male and two were females. Interval of onset of development of TD in these patients was in the range of 4 months to 5 years. In these reported cases it was clearly demonstrated that there is a cause and effect relationship of risperidone or olanzapine with tardive dyskinesia.

These published reports had some limitations which posed difficulties in analysis of these cases. The use of polypharmacy in some cases was adopted. No long term drug free observation period or rechallenge with the provoking drug was used in these reports. Precise information was not available in few cases. Thus findings cannot be generalized.

But we cannot ignore the significance of these reports and these raise the level of concern in an important clinical problem. The role of these drugs in induction of tardive dyskinesia requires more clarification.

As the best treatment of tardive dyskinesia is prevention only and these reported cases suggest the need for judicious use of risperidone and olanzapine in clinical practice. Regular monitoring for the development and early diagnosis of tardive dyskinesia is needed. Careful assessment is warranted when schizophrenic patient are given maintenance therapy with these drugs. Their use in behavioural subjects in the absence of psychosis should be avoided. Promise of atypical antipsychotics being safer drug is being challenged and will be clear in the next few years. There has been insufficient duration of experience and adequate follow-up with risperidone or olanzapine to test the hypothesis that they have a low prevalence of tardive dyskinesia. More intensive research and long term studies in the future are needed to address the various issues raised by these case reports.

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