Newer antipsychotics and the rabbit syndrome
Mario Catena Dell’Osso*1,2, Andrea Fagiolini3, Francesca Ducci2,4, Azadeh Masalehdan3, Antonio Ciapparelli2 and Ellen Frank3

Address: 1Dipartimento di Scienze Neurologiche e Psichiatriche, University of Florence, Florence, Italy, 2Dipartimento di Psichiatria, Neurobiologia, Farmacologia e Biotecnologie, University of Pisa, Pisa, Italy, 3Department of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania, USA and 4National Institutes of Health, Bethesda, USA

Email: Mario Catena Dell’Osso* - catena.mario@virgilio.it; Andrea Fagiolini - fagioliniA@upmc.edu; Francesca Ducci - duccif@mail.nih.gov; Azadeh Masalehdan - masalehdanag@upmc.edu; Antonio Ciapparelli - ciapparelli.a@tiscali.it; Ellen Frank - frankE@upmc.edu

* Corresponding author

Abstract

Background: Rabbit syndrome is a movement disorder that is associated with long-term exposure to neuroleptic medications. Of particular interest and importance is the risk of rabbit syndrome with exposure to the newer atypical antipsychotics. Our recent experience with such a case brought to light the importance of exploring this risk.

Methods: MEDLINE and PubMed (1972–2006) databases were searched for English language articles using the keywords rabbit syndrome, tardive dyskinesia, antipsychotic, extrapyramidal symptoms and side effects. A recent case study is used to expand upon the literature available on newer antipsychotics and rabbit syndrome.

Results: We reviewed papers that addressed the following aspects of rabbit syndrome 1) the clinical manifestations 2) prevalence and risk factors, 3) etiopathogenesis 4) older antipsychotics and rabbit syndrome 5) newer antipsychotics, 6) treatment options. Moreover, we report a case of RS in a 50 year old white female, diagnosed with bipolar I disorder, that, after the discontinuation of risperidone, developed involuntary movements of the mouth that were fine, rhythmic and rapid, along the vertical axis, and without involvement of the tongue. After the re-introduction of risperidone, the symptoms decreased in a few hours and disappeared after 3 days.

Conclusion: Eleven cases of rabbit syndrome have been documented since the implementation of newer antipsychotics. Future research is needed to better understand the etiopathogenesis of rabbit syndrome in psychiatric populations treated with the atypical antipsychotics. Understanding the differences and similarities of rabbit syndrome and tardive dyskinesia is crucial to the creation of a successful treatment paradigm.

Background

Rabbit syndrome (RS) is characterized by fine, rapid, rhythmic movements along the vertical axis of the mouth. Long-term exposure to the older neuroleptics has clearly been associated with RS, but little is known regarding the risk of RS due to the exposure to the newer atypical antipsychotics. This syndrome is considered a distinct neuroleptic-induced extrapyramidal syndrome. There is...
evidence that RS combines features of both Parkinson’s disease and tardive dyskinesia [1-4].

In the present study we review the current knowledge on the clinical manifestations, the etiopathogenesis, and the prevalence of the RS. We also report on a patient who developed the syndrome after discontinuing an atypical antipsychotic, comment on the few similar cases that have been recently published, and review the possible treatment options and the outcome of patients developing this syndrome.

Methods
MEDLINE and PubMed (1972–2006) databases were searched for English language articles using the keywords rabbit syndrome, tardive dyskinesia, antipsychotic, extrapyramidal symptoms. We also performed a chart review for the case of RS that occurred in one of our patients upon discontinuation of an atypical neuroleptic.

Results and discussion
Clinical manifestations
RS is characterized by fine, rapid, rhythmic movements along the vertical axis of the mouth. These involuntary movements occur at a frequency of approximately 5 Hz. The oral movements are often accompanied by a popping sound that is produced by the rapid smacking on one’s lips. This syndrome is limited exclusively to the territory of the oral and masticatory muscles and does not involve the tongue [1]. The pattern of movement contrasts tardive dyskinesia (TD), another form of oral dyskinesia, in which the tongue is involved in making slower and less regular movements.

Similar to TD, the movements of RS increase in situations of fatigue and anxiety. Stressful situations may also be a trigger for intensifying the symptoms of RS. RS always worsens during attention, concentration, and motor performances. In these situations, RS is accompanied by an increase in muscle tone. Jus et al. [5] found that when patients were asked to follow a labyrinth pattern with a pencil, RS symptoms intensified. Different from other types of oral dyskinesias such as buccolingual and buccolinguo-masticatory syndromes, RS cannot be suppressed voluntarily by the patient [6]. RS can be associated with drug-induced parkinsonism [7,8] and TD [3,9]. RS symptoms are similar to Parkinson’s symptoms in their persistence during stage 1 non-REM sleep, whereas a cessation of symptoms is observed in the same situation with TD.

Prevalence and risk factors
RS is believed to be a rare condition affecting only a small fraction of the psychiatric population using neuroleptics. Yassa and Lal [8] carried out the first prevalence study by focusing on the inpatient population of a psychiatric insti-
tution and reported a 2.3% prevalence rate of RS in a sample of 266 inpatients receiving older neuroleptics, either as monotherapy or in combination with anticholinergic agents. The prevalence rate of RS in patients solely taking neuroleptics was 4.4%. Another prevalence study [10] found a rate of 1.5% for RS among neuroleptic-treated patients in a geriatric mental health clinic. To the best of our knowledge, no prevalence study has been published to date on the relationship between RS and atypical antipsychotics.

Gender and age are also believed to be related to the development of RS. This syndrome is found predominantly in middle-aged and elderly patient populations [11]; women are also believed to be at higher risk for developing RS than their male counterparts [7]. Data from Tables 1 and 2 indicates that most of the cases of RS reported to-date have involved patients with a diagnosis of schizophrenia. Previous brain damage has also been associated with RS [1].

Etiopathogenesis
RS may appear during treatment with neuroleptic medications or after discontinuation of such medicines. The mechanisms triggering RS are believed to be similar to those involved in the pathogenesis of the neuroleptic-induced Parkinsonian syndrome [7]. In fact, RS may be due to a hypercholinergic state resulting from the neuroleptic blockade of dopaminergic neurons in the extrapyramidal system [12]. This would explain the response of RS to anticholinergic drugs [3,13].

Nishiyama [14], however, reported a case of RS that was treated successfully using haloperidol in a woman affected by multiple system atrophy. In this case, the etiopathogenic mechanism of RS may be similar to TD, possibly suggesting a state of cholinergic hypofunction due to a denervation-type dopaminergic hypersensitivity in the basal ganglia [15].

Given that the disease mechanism of RS resembles the mechanism of parkinsonism and the mechanism of TD, it may be possible to attribute RS to an imbalance of the cholinergic and dopaminergic function in the basal ganglia. However, the etiopathogenesis of RS, parkinsonism, and TD, are still unclear.

Interestingly, neuroleptic exposure was found to be unrelated to following six documented cases of RS [11,16-18,20]. Truong [16] described a case of RS observed in a 76-year-old female who had undergone brain surgery 16 years earlier. Kamijo [17] reported a case related to ingestion of a massive quantity of phenol in a suicide attempt. Phenol intoxication may have caused RS by inducing cholinergic dominance in the central nervous system. RS
was also observed in patients treated with imipramine, citalopram, paroxetine and methylphenidate [11,18-20]. It is possible that these antidepressants, potent inhibitors of serotonin reuptake, caused RS through a serotonin-mediated inhibition of dopaminergic neurotransmission in the basal ganglia in predisposed subjects [21,22].

**Older antipsychotic medications and Rabbit Syndrome**

Several case studies have been published on the relationship between older antipsychotics and RS (table 1). The use of high-potency neuroleptics with low anticholinergic activity, like haloperidol, is common to most of these cases. In fact, of the 34 cases reported in the literature, 12 were associated with haloperidol, and 8 with piperazinic phenothiazines (Fluphenazine, Perphenazine, Trifluoperazine). These high-potency drugs are known for a relative high tendency to induce parkinsonism [23]. This evidence, coupled with the fact that some patients who developed RS reported a previous history of the more usual parkinsonian side-effects [13], substantiates the hypothesis that RS and drug-induced parkinsonism may be mediated by a neuroleptic blockade of the same pool

| Patient | Age | Gender | Diagnosis | Duration of previous antipsychotic treatment | Drug (mg) | Parkinsonian Symptoms | Tardive Dyschinesia |
|---------|-----|--------|-----------|---------------------------------------------|-----------|----------------------|---------------------|
| Patient 1 [1] | 66 | F | Schizophrenia | Several years | Perphenazine (8) | No | No |
| Patient 2 [1] | 67 | F | Schizophrenia | Several years | Trifluoperazine (5) | Yes | Yes |
| Patient 3 [1] | 54 | F | Schizophrenia | Several years | Chlorpromazine (50) | Yes | No |
| Patient 4 [1] | 66 | M | Schizophrenia | Several years | Trifluoperazine (5) | No | No |
| Patient 5 [1] | 47 | M | Schizophrenia | Several years | Thioridazine (100) | Yes | No |
| Patient 6 [2] | Between 47 and 62 | M | - | Several years | - | No | No |
| Patient 7 [2] | Between 47 and 62 | M | - | Several years | - | No | No |
| Patient 8 [2] | Between 47 and 62 | F | - | Several years | - | No | No |
| Patient 9 [2] | Between 47 and 62 | F | - | Several years | - | No | No |
| Patient 10 [2] | Between 47 and 62 | F | - | Several years | - | No | No |
| Patient 11 [2] | Between 47 and 62 | F | - | Several years | - | No | No |
| Patient 12 [3] | 54 | F | Schizophrenia | 10 years | Fluphenazine decanoate (25) | No | Yes |
| Patient 13 [25] | 62 | F | Schizophrenia | 18 months | Mesoridazine (100) | No | No |
| Patient 14 [25] | 68 | F | Schizophrenia | 10 years | Thioridazine (25) | Yes | No |
| Patient 15 [28] | 63 | F | Schizophrenia | Several | Fluphenazine decanoate Fluphenazine (20) | Yes | No |
| Patient 16 [28] | 66 | M | Bipolar disorder | 8 days | Haloperidol (240) | Yes | No |
| Patient 17 [8] | 42 | F | Schizophrenia | 16 months* | Haloperidol (90) | Yes | - |
| Patient 18 [8] | 50 | F | Schizophrenia | 9 months* | Haloperidol (10) | No | - |
| Patient 19 [8] | 57 | M | Schizophrenia | 7 months* | Haloperidol (8) | Yes | - |
| Patient 20 [8] | 67 | F | Bipolar disorder | 8 months* | Haloperidol (8) | - | - |
| Patient 21 [8] | 71 | F | Korsakoff's syndrome | 12 months* | Haloperidol (8) | - | - |
| Patient 22 [8] | 77 | M | Mental retardatio | 12 months* | Haloperidol (7) | Yes | - |
| Patient 23 [12] | 52 | M | Schizophrenia | 20 years | - | No | No |
| Patient 24 [13] | 75 | M | Schizophrenia | 30 years | Trifluoperazine (15) | No Just | No |
| Patient 25 [7] | 63 | F | Schizophrenia | 11 years | Haloperidol (8) | Yes | No |
| Patient 26 [7] | 63 | F | Schizophrenia | 32 years | Propriecaine (50) | Yes | - |
| Patient 27 [7] | 44 | F | Schizophrenia | 13 years | Haloperidol (5) | Yes | No |
| Patient 28 [7] | 48 | F | Schizophrenia | 31 years | Haloperidol (5) | Yes | No |
| Patient 29 [7] | 58 | M | Schizophrenia | 11 years | Haloperidol (5) | Yes | No |
| Patient 30 [10] | 77 | F | Schizophrenia | 15 months | Thioridazine (75) | No | No |
| Patient 31 [4] | 57 | F | Acute paranoid episode | 19 months | Haloperidol (30-50) | No | No |
| Patient 32 [29] | 31 | F | Schizophrenia | 14 years | Haloperidol (5) | No | No |
| Patient 33 [26] | 28 | F | Schizophrenia | 5 years | Zuclopentixol (200) | No | No |
| Patient 34 [19] | 65 | F | Major depression | 10 years | Paroxetine (2) | No | No |

Patients identified by MEDLINE database search in December 2006.
of dopaminergic neurons in the extrapyramidal system [3].

**Newer antipsychotic medications and the Rabbit Syndrome**

To our knowledge, there are 10 reported cases of RS related to newer antipsychotics (table 2). Seven of the ten reported cases of RS are linked to risperidone. Risperidone is considered to be the atypical antipsychotic with the highest incidence of extrapyramidal symptoms [24]. This high incidence may be caused by the high affinity for the serotonin type 2 and dopamine type 2 receptors and the low affinity for cholinergic muscarinic receptors.

The three remaining cases occurred with clozapine, olanzapine and aripiprazole, respectively. These atypical antipsychotics are characterized by a relatively low incidence of extrapyramidal symptoms. It is interesting that, in the case induced by clozapine, TD preceded RS, which was developed after treatment for approximately 2 years with chlorpromazine, haloperidol, and fluphenazine decanoate, either in monotherapy or in combination.

We have observed a case of RS in a 50 year old white female. The patient was diagnosed with bipolar I disorder and was treated with lithium, gabapentin, lorazepam, risperidone, and citalopram. Though the intended treatment regimen was outpatient, the patient was hospitalized as a result of a severe depressive episode in which she was unable to care for herself physically. At the time of her admission, the dose of risperidone was 4 mg/day. Because of a shuffling gait, moderate drooling, and cog wheeling rigidity, the risperidone was first decreased to 1 mg and, after 1 day, it was completely discontinued. This led to a quick resolution of the extrapyramidal symptoms. No changes were made in her psychopharmacological treatment except for an adjustment of the lithium dose and the addition of trazodone. About 10 days after the discontinuation of risperidone, the patient developed involuntary movements of her mouth. The movements were fine, rhythmic, and rapid, along the vertical axis, and without lingual involvement. A diagnosis of risperidone withdrawal emergent RS was made. Risperidone was re-started at 1.5 mg/day. The symptoms noticeably decreased after a few hours and completely disappeared after 3 days. No extrapyramidal symptoms were observed.

**Treatment Options**

Differently from TD, RS typically responds favorably to anticholinergic agents such as benztropine, biperiden, procyclidine and trihexyphenidyl [3]. RS typically disappears a few days after the introduction of an anticholinergic agent [4], but can, on occasion, reappear after stopping anticholinergic medications [12]. Researchers opted to implement a new treatment strategy after evidence was found that some patients with RS treated with an anticholinergic agent later developed TD [3,4,25]. The availability of the newer atypical antipsychotics has led to the implementation of additional treatment strategies.

Durst [26] successfully treated RS triggered by the typical neuroleptic zuclopenthixol by switching the patient from zuclopenthixol to olanzapine. After the administration of olanzapine (started at 5 mg/day and titrated up to a target dose of 10 mg/day), both the RS and the psychotic symptoms that the patient was presenting showed significant improvement. In another report, risperidone-induced RS not responsive to anticholinergic agents, disappeared after switching the patient to quetiapine. After 4 weeks of quetiapine treatment (starting dose of 100 mg/day and titration up to 700 mg/day) rabbit movements diminished significantly with further improvements during the follow-up period [27]. Switching to a new atypical antipsychotic with high anti-cholinergic properties, like olanzapine or clozapine, may be another possible treatment strategy for RS [24].

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**Table 2: Newer Antipsychotics and the Rabbit Syndrome.**

| Patient 1 [30] | 68 F | Schizophrenia | Risperidone (4) | 4 months | No | No |
| Patient 2 [31] | 27 M | Schizophrenia | Risperidone (4) | 7 months | No | No |
| Patient 3 [32] | 38 M | Schizophrenia | Risperidone (4) | 8 months | No | No |
| Patient 4 [33] | 38 M | Major depression with psychotic features | Risperidone (4) | 4 months | No | No |
| Patient 5 [34] | 48 F | Schizophrenia | Clozapine (225) | 7 months | No | Yes |
| Patient 6 [35] | 29 F | Schizophreniform disorder | Aripiprazole (10) | 6 weeks | Yes | No |
| Patient 7 [36] | 56 M | Major depression with psychotic features | Risperidone (6) | 4 months | Yes | No |
| Patient 8 [27] | 22 M | Schizophrenia | Biperiden (2) | 12 months | Yes | No |
| Patient 9 [37] | 42 F | Bipolar I disorder | Risperidone (4) | 3 weeks | No | No |
| Patient 10 [38] | 74 - | Bipolar disorder | Olanzapine (20) | - | - | - |
| Patient 11 (our case) | 50 F | Bipolar I disorder | Risperidone (decreased from 4 to 1 and discontinued) | 3 months | Yes | No |
Conclusion
Since Villeneuve first described RS in 1972 it has been associated with long-term exposure to the older neuroleptics (table 1). In the recent past RS was also observed in patients treated with the newer antipsychotics. To date, 11 cases, including the one documented in this paper, of RS have been reported in patients treated with atypical antipsychotics. Of these 11 cases, seven were related to the use or discontinuation of risperidone (table 2). The pharmacodynamics of risperidone may explain its tendency to induce RS. Although the possibility of RS should always be considered in patients treated with atypical neuroleptics in general, and with risperidone in particular, it is important to note that there is a low incidence of this syndrome.

RS can be successfully treated. RS responds well to treatment with anticholinergic agents, whereas TD would be worsened by such a treatment regimen. Conversely the use of dopamine depleters like reserpine, which have proven effective with TD, may worsen RS. Once again, this underscores the importance of distinguishing between these two syndromes. RS can be distinguished from typical oral dyskinesias because the movements observed in the latter are slower and less regular, involve the tongue, can be suppressed voluntarily by the patient, and do not persist during stage I non-REM sleep.

Abbreviations
RS, rabbit syndrome
TD, Tardive dyskinesia

Authors’ contributions
MCDO conceived of the study and participated in its design and coordination. AF participated in the design of the study and gave the informations about the new reported case. FD and AC participated in the review of the literature and drafted the manuscript. AM participated in the review of the literature and drafted the manuscript. EF participated in the design of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

References
1. Villeneuve A. The rabbit syndrome. A peculiar extrapyramidal reaction. Can Psychiatr Assoc J 1972, 17(2):556-572.
2. Jus K, Jus A, Villeneuve A, Pires P, Pineau R, Villeneuve R: Studies on the action of certain pharmacological agents on tardive dyskinesia and on the rabbit syndrome. Int J Clin Pharmacol 1974, 9:138-145.
3. Sovner R, Dimascio A: The effect of benztriptine mesylate in the rabbit syndrome and tardive dyskinesia. Am J Psychiatry 1977, 134:1301-1302.
4. Schwartz M, Weller B, Erdreich M, Sharf B: Rabbit syndrome and tardive dyskinesia: two complications of chronic neuroleptic treatment. J Clin Psychiatry 1995, 56:212.
5. Jus K, Jus A, Villeneuve A, Villeneuve R: Influence of concentration and motor performance on tardive dyskinesia and rabbit syndrome. Can Psychiatr Assoc J 1973, 18:317-320.
6. Jus K, Villeneuve A, Jus A: Tardive dyskinesia and the rabbit syndrome during wakefulness and sleep. Am J Psychiatry 1972, 129:765.
7. Wada Y, Yamaguchi N: The rabbit syndrome and antiparkinsonian medication in schizophrenic patients. Neuropsychobiology 1992, 25:149-152.
8. Yassa R, Lal S: Prevalence of the rabbit syndrome. Am J Psychiatry 1986, 143:656-657.
9. Jus K, Jus A, Villeneuve A: Polygraphic profile of oral tardive dyskinesia and of rabbit syndrome: for quantitative and qualitative evaluation. Diseases of the Nervous System 1973, 34:27-32.
10. Chiou HF, Lam LC, Chung DW, Wing YK, Shum PP: Prevalence of the rabbit syndrome in Hong Kong. J Nerv Ment Disord 1993, 181:264-265.
11. Mandazzri L, Ichiise M, Remington G, Smith R: Rabbit syndrome, antidepressant use and cerebral perfusion SPECT scan findings. J Psychiatr Neurosci 1991, 16(4):227-229.
12. Deshmukh DK, Joshi VS, Agarwal MR: Rabbit syndrome: a rare complication of long-term neuroleptic medication. Br J Psychiatry 1990, 157:293.
13. Almeida JH: Neurololgic side-effects The “rabbit syndrome”. Int J Geriatr Psychiatry 1991, 6:537-539.
14. Nishiyama K, Masuda N, Kurisaki H: A case of rabbit syndrome – its unique pharmacological features. Rinsho Shinkeigaku 1993, 33:663-665.
15. Gerlach J, Reisby N, Randrup A: Dopaminergic hypersensitivity and cholinergic hypofunction in the pathophysiology of tardive dyskinesia. Psychopharmacol 1974, 34(1):21-35.
16. Truong DD, Hermanowicz N, Mistura K: Rabbit syndrome treated with botulinum toxin. South Med J 1990, 83:854-855.
17. Kamijo Y, Soma K, Fukuda M, Asari Y, Ohwada T: Rabbit syndrome following phenol ingestion. J Toxicol Clin Toxicol 1999, 37:509-511.
18. Parvin MM, Swartz CM: Dystonic rabbit syndrome from citalopram. Clin Neuropsychopharmacol 2005, 28:289-291.
19. Gouras P, Argyriou AA, Bakalioud C, Beratis S: Induction of the rabbit syndrome following coadministration of paroxetine, perphenazine, and amitriptyline. Clin Neuropsychopharmacol 2004, 27:299-300.
20. Mendoza RN, Duggal HS: Methylphenidate-induced rabbit syndrome. Ann Pharmacother 2006, 40:2076.
21. Leonard BE: Pharmacological effects of serotonin reuptake inhibitors. J Clin Psychiatry 1988, 49:12-17.
22. Kim SW, Dysken MW: Potential antidopaminergic effects of serotonin reuptake inhibitors. J Clin Psychiatry 1991, 52:42.
23. Schwartz JT, Brotman AW: A clinical guide to atypical antipsychotics. Drugs 1992, 44:981-992.
24. Tarsy D, Baldessarini RJ, Tarazi FI: Effects of newer antipsychotic on extrapyramidal function. CNS Drugs 2002, 16:23-45.
25. Weiss KJ, Ciraulo DA, Shader RI: Phystostigmine test in the rabbit syndrome and tardive dyskinesia. Am J Psychiatry 1980, 137:627-628.
26. Durst R, Katz G, Ziljin J, Raskin S, Kalman I: Rabbit syndrome treated with olanzapine. Br J Psychiatry 2000, 176:193.
27. Akindag A, Yanik M: A case of rabbit syndrome treated with quetiapine. Eur Psychiatry 2005, 20:574-575.
28. Todd R, Lippman S, Manshadi M, Chang A: Recognition and treatment of rabbit syndrome, an uncommon complication of neuroleptic therapies. Am J Psychiatry 1983, 140:1519-1520.
29. Damentaran SS, Thakammar JK: Reversal of rabbit syndrome with olanzapine. Aust N Z J Psychiatry 2000, 34:172-173.
30. Schwartz M, Beny A, Sharf B: Risperidone-induced rabbit syndrome. Br J Psychiatry 1998, 173:267-268.
31. Levin T, Heresco-Levy U: Risperidone-induced rabbit syndrome: an unusual movement disorder caused by an atypical antipsychotic. Eur Neuropsychopharmacol 1999, 9:137-139.
32. Nashimura K, Tsuka M, Horikawa N: Withdrawal-emergent rabbit syndrome during dose reduction of risperidone. Eur Neuropsychopharmacol 2001, 11(4):323-324.
33. Hoy JS, Alexander B: Rabbit syndrome secondry to risperidone. Pharmacotherapy 2002, 22:13-15.
34. Sehit S, Bhargava SC: Clozapine-induced rabbit syndrome. J Clin Psychiatry 2003, 64:219.
35. Mendhekar DN: Aripiprazole-induced rabbit syndrome. *Aust N Z J Psychiatry* 2004, 38:561.
36. Eren I, Ozcankaya R, Altinyazar V: Risperidone-induced rabbit syndrome in mood disorder. *Eur Psychiatry* 2004, 19:452-453.
37. Mendhekar DN: Rabbit Syndrome induced by combined lithium and risperidone. *Can J Psychiatry* 2005, 50:369.
38. Sabolek M, Bayerle M: Rabbit syndrome due to olanzapine. *Psychiatr Prax* 2005, 32:202-204.