

Treatment of paradoxical insomnia with atypical antipsychotic drugs

A comparison of olanzapine and risperidone

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ABSTRACT

الأهداف: مقارنة فعالية دوائين مضادين للذهان اولانزابين وريزبريدون لعلاج الأرق التناقضي.

الطريقة: أجريت دراسة مقطعية على 29 مريض مصاب بالأرق التناقضي تم تشخيصهم بالمقابلة النفسية وجهاز قياس النشاط قسموا بشكل عشوائي إلى مجموعتين. تم علاج المجموعة الأولى عددها=15 شخص باستخدام 10 ملغرام اولانزابين يومياً بينما عولجت المجموعة الثانية باستخدام ريزبريدون 4 ملغرام يومياً عددها=14 ولمدة 8 أسابيع. كما أكمل جميع المرضى اختبار نوعية النوم (PSQI) للحد الأساسي في نهاية الدراسة.

النتائج: كما هو متوقع أظهر تحليل النشاط الأساسي أن الوقت الإجمالي للنوم لم يكن مهم بشكل إحصائي $p < 0.3$ بين مجموعتي العلاج. ولكن تطورت نوعية النوم مع العلاج بشكل إحصائي $p < 0.001$. عند مقارنة اتجاه العلاج كان هنالك تحسن واختلاف مهم إحصائي بين المجموعتين بناء على بيانات اختبار نوعية النوم (9.21+2.35, 6.07+4.46). كما أن المرضى الذين عولجوا بعقار اولانزابين تحسّنوا بشكل ملحوظ بالمقارنة مع المرضى الذين تم علاجهم بعقار ريزبريدون $p < 0.04$.

خاتمة: أظهرت هذه الدراسة أن الأدوية المضادة للذهان مثل اولانزابين وريزبريدون تعد من الخيارات المفيدة لعلاج الأرق التناقضي. نحتاج إلى المزيد من الدراسات السريرية بفترة أطول ومراجعة دورية.

Objective: To compare the efficacy of 2 atypical antipsychotic drugs, olanzapine and risperidone, in the treatment of paradoxical insomnia.

Methods: In this cross-sectional study over a 2-year period (September 2008 to September 2010), 29

patients with paradoxical insomnia, diagnosed in Kermanshah, Iran by both psychiatric interview and actigraphy, were randomly assigned to 2 groups. For 8 weeks, the first group (n=14) was treated with 10 mg olanzapine daily, and the second group (n=15) was treated with 4 mg risperidone daily. All participants completed the Pittsburgh Sleep Quality Inventory (PSQI) at baseline and at the end of the study.

Results: As expected, a baseline actigraphy analysis showed that total sleep time was not significantly different between the 2 treatment groups ($p < 0.3$). In both groups, sleep quality was improved ($p < 0.001$) with treatment. When comparing the 2 treatments directions, a significant difference emerged (9.21±2.35, 6.07±4.46) among the 2 treatment groups based on data from the PSQI. Patients who were treated with olanzapine showed greater improvement than patients who were treated by risperidone ($p < 0.04$).

Conclusion: Atypical anti-psychotic drugs such as olanzapine and risperidone may be beneficial options for treatment of paradoxical insomnia. Larger clinical trials with longer periods of follow-up are needed for further investigation.

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Insomnia is a common sleep disorder characterized by difficulties initiating or maintaining sleep, or both. Approximately one-third of the general population experience some form of insomnia.^{1,2} Insomnia, which affects quantity and quality of sleep, has adverse consequences on overall health and quality of life. As a result, there are significant daytime impairments such as fatigue, irritability, and decreased cognitive functioning.³ Insomnia may be a precursor for psychiatric disorders such as depression and anxiety disorders, if left untreated.⁴ Therefore, treatment of insomnia is crucial for improving health and quality of life.³⁻⁶ Paradoxical insomnia, otherwise known as sleep state misperception, is a subtype of insomnia with considerable challenges related to diagnosis and treatment. Patients with paradoxical insomnia present with complaints of insufficient amounts of sleep due to difficulties initiating and maintaining sleep. However, the hallmark of this type of insomnia is that these complaints are not substantiated by objective measures such as polysomnography, which typically shows an adequate amount of nocturnal sleep of good quality. In the International Classification of Sleep Disorders, Second Version, the diagnostic criteria for sleep state misperception include: a) person complains of insomnia, b) sleep duration and quality are normal, c) polysomnographic monitoring demonstrates normal sleep latency, normal number of arousals, and normal sleep duration with or without a multiple sleep latency test that demonstrates a mean sleep latency of greater than 10 minutes, d) no medical or mental disorder produces the complaint, and e) other sleep disorders producing insomnia are not present to the degree that would explain the patients complaint.⁷ The exact pathophysiology of the condition has not been identified.⁸⁻¹¹ It has been proposed that anxiety may provoke paradoxical insomnia, and that ruminative worry about not sleeping exaggerates the condition. Paradoxical insomnia may represent a somatic delusion or hypochondriasis. Delusional disorder somatic type is referred to as monosymptomatic hypochondriacal psychosis. If the degree of reality impairment for patients with paradoxical insomnia is high and the patient's beliefs regarding insomnia are fixed, and present intensely it may be possible that this clinical description is actually a somatic type of delusional disorder.¹²

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However, this disorder can occur in individuals who are free from psychopathology. Overall, little is known about this form of insomnia, and efficacious treatments have not been established. Although a general insomnia treatment protocol is often recommended, there is a lack of research evaluating its efficacy, and a well-established treatment protocol is not available to date. We recently published a case study in which a 60-year-old woman presented with paradoxical insomnia that did not respond to typical insomnia treatments (namely, trazodone and other tranquilizers).¹³ She presented with high level of agitation, endorsed suicide ideation due to her insomnia, and did not respond to electro convulsive therapy (ECT). After a thorough evaluation that included actigraphy to objectively document her sleep time and patterns, we successfully treated her paradoxical insomnia with an antipsychotic drug, olanzapine. This result prompted us to propose that there may be a subtype of paradoxical insomnia with psychotic features.¹³ Off-label use of atypical antipsychotic drugs (including olanzapine and risperidone) has been found to improve sleep quality in both healthy patients and patients with psychotic disorders, such as schizophrenia.¹⁴⁻²⁰ On the other hand, there is supporting evidence that atypical anti psychotics may be helpful in the treatment of different types of delusions, including somatic delusions.¹⁶⁻¹⁸

In clinical practice, we have found that some patients have failed to respond to typical treatment with benzodiazepine agents. Therefore, considering the efficacy of atypical antipsychotic drugs on both sleep quality and somatic delusion, and our clinical experience with the case described above, our hypothesis was that atypical antipsychotics, such as olanzapine and risperidone, may be viable treatment options for paradoxical insomnia. The study aimed to compare efficacy of these 2 drugs in the treatment of paradoxical insomnia. Thus, the efficacy of each of the 2 drugs, and a comparison of them with each other was possible. Most clinicians consider antipsychotic drugs the treatment of choice for delusional disorder. Hence, we used antipsychotic drugs for treatment. Atypical antipsychotic drugs are reportedly more effective and have fewer side effects than traditional antipsychotics. Consistent with the drug of choice in our prior report,¹³ we used olanzapine in the current study as well as another drug we chose to evaluate. One of the side effects of olanzapine is sedation and somnolence.¹⁶ As this side effect is less frequent with risperidone, we chose risperidone as the comparative drug.

Methods. Study procedures. The study was approved by the ethics board of Kermanshah Medical University (KUMS) in Kermanshah, Iran, and was conducted from September 2008 to September 2010. Patients were consecutively enrolled at the KUMS Sleep Research Center. All patients were referred for complaints of insomnia and were subsequently diagnosed with paradoxical insomnia by psychiatric interview and actigraphy. Interestingly, all participants in the study presented with complaints of severe insomnia. Participants did not present with other complaints or symptoms of other co-morbid psychiatric disorders. Although we did not formally assess the consequences of paradoxical insomnia disorder on daily life of the participants with a standardized measure, all participants reported complaints of discomfort and fatigue in clinical interview. Participants with other sleep disorders (such as sleep apnea) were excluded. Actigraphy was used to objectively measure total sleep time and quality of sleep for 72 consecutive hours. Normal sleep as measured by actigraphy was an inclusion criterion, as complaints of insomnia must be inconsistent with actual objective data. We used the following criteria for inclusion based on actigraphy data: a) sleep latency of less than 15 minutes, b) sleep efficiency of more than 85%, and c) total sleep time of greater than 7 hours. As often found with this type of insomnia, when participants were given feedback regarding their normal sleep, they did not respond to feedback and continued to perceive they were not sleeping adequately. After providing informed consent, patients were randomly assigned to one of 2 treatment groups. We used the same antipsychotic treatment dosage as in our prior study.¹³

Participants in the first group were treated with olanzapine (10 mg daily), and participants in the second group were treated with risperidone (4 mg daily) for 8 weeks. We used the dose, and titration guidelines recommended for psychotic disorders.²¹⁻²⁴ Olanzapine is an antagonist of serotonin 5 hydroxy tryptophan 2a (5-HT_{2A}) and dopamine D₂, and an antagonist of the D₁, D₄, Alpha 1, 5-HT_{2A}, muscarinic M₁ through M₅ and the histamine H₁ receptors. The initial dose for treatment is typically between 5-10 mg. After one week, the dosage can be raised to 10 mg a day.²¹⁻²⁴ Risperidone is an antagonist of serotonin 5-HT_{2A}, dopamine D₂, Alpha 1 and Alpha 2 adrenergic, and histamine H₁ receptors. The initial dosage is usually 1-2 mg at night, which can then be raised to 4 mg per day. Positron emission tomography (PET) studies have shown that a dosage from 1-4 mg per day provides the required D₂ blockade needed for a therapeutic effect.²¹⁻²⁴ The treatment lasted 8 weeks. A safety

analysis was conducted after 2 weeks, during which all participants were clinically assessed for any adverse side effects of drugs. No adverse effects were found, and the intervention continued for 8 weeks. Clinical assessments for metabolic side effects (such as diabetes) were performed periodically.

Both olanzapine and risperidone are produced by several Iranian manufactures (such as Bakhtarshimi, Exir, Pharmaceutical Company, Sobhan Darue, and DR Abidi), which are under the supervision of the Iran Ministry of Health and Medical Education. There is no evidence to support better efficacy of production of one manufacturer from the others. The drugs administered in this study were manufactured by Bakhtarshimi, Kermanshah, Iran.

Participants. Thirty patients with paradoxical insomnia were diagnosed with psychiatric interview and actigraphy.²⁵ Patients with other psychiatric disorders, chronic medical disorders, and substance disorders were excluded. Other drugs that might have an interactive effect with our drugs were stopped for at least 2 weeks (namely, benzodiazepines, antihistamine, and any other drug with a narcotic effect). All but one participant (due to his immigration from Kermanshah city) completed the study for a total of 29 participants (olanzapine, n=14, risperidone, n=15). Figure 1 summarizes the study protocol.

Measures. Sleep quality was assessed at baseline and at the end of 8 weeks using the Pittsburgh Sleep

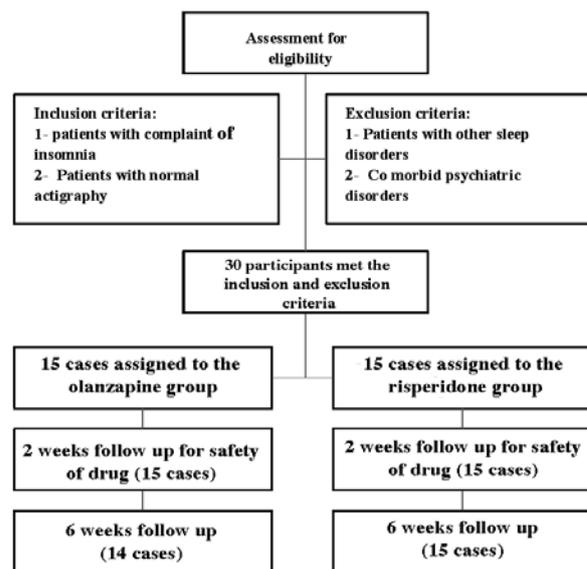


Figure 1 - The study protocol for comparison of the efficacy of 2 antipsychotic drugs on the sleep quality of Iranian paradoxical insomnia patients.

Table 1 - Demographic data of Iranian paradoxical insomnia patients.

Variable	Total sample (n=29)	Olanzapine group (n=14)	Risperidone group (n=15)	Statistical test*	P-value
Age, mean±SD	53.4±14.4	56.7±14.87	50.93±13.94	1.18	0.23
<i>Gender, n (%)</i>				0.29	0.43
Male	13 (44.8)	7 (50.0)	6 (40.0)		
Female	16 (55.2)	7 (50.0)	9 (60.0)		
<i>Education level, n (%)</i>				0.33	0.84
No formal education	11 (37.9)	6 (42.9)	5 (33.3)		
Under diploma	13 (44.8)	6 (42.9)	7 (46.7)		
Diploma and graduate	5 (17.2)	2 (14.3)	3 (20.0)		
Baseline total sleep time, mean±SD	8.04±0.52	8.007±0.51	8.073±0.54	0.36	0.60
Sleep efficiency, mean±SD	86.8±2.04	87.2±2.08	86.4±2.00	1.02	0.07

*Chi-square used for most analyses, Fisher exact test used if a cell size was less than 5; t-test was used for age

Quality Index (PSQI). The PSQI is a well-validated instrument that provides a total score that is an estimate of overall sleep quality and ranges from no sleep difficulties to severe difficulties. The validity and reliability have been established in multiple studies (Cronbach's alpha >0.80). The scale also yields 7 domains (sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, sleep medications, and daytime dysfunction). Higher scores on the PSQI indicate poorer sleep quality and a higher level of sleep disturbance. The maximum score that can be obtained is 21. For this study, we considered scores greater than 5 as indicative of fragmented sleep of poor quality.²⁶⁻²⁹ In Iran in 2009, Farrahi et al²⁹ studied the validity and reliability of the PSQI when translated in Persian, and found the Cronbach's alpha coefficient to be 0.89. Using a cutoff of 7/8, the sensitivity was reported as 100% and specificity was reported as 93%.

Statistical analyses. Data were collected and analyzed by Stata software 8th version (StataCorp LP, College Station, TX, USA). First, the demographic variables

and PSQI-1 and PSQI-2 total scores were computed and were then compared using t-test, chi-square analysis, and Mann-Whitney test (age by t-test, gender and education by chi-square, PSQI-1 and PSQI-2 in both groups by paired t-test and mean difference of PSQI in both groups for comparison of 2 drugs by Mann-Whitney test). An alpha value of 0.05 was used study-wide to denote statistical significance.

Results. The demographic characteristics of participants in each of the treatment groups are depicted in Table 1. Participant groups did not differ significantly on variables of age ($p=0.23$), gender ($p=0.43$) or education ($p=0.84$). Significant differences were found between the sleep quality in the 2 groups, both olanzapine and risperidone, after intervention. Comparison of the 2 groups showed that sleep quality was more improved by olanzapine ($p=0.04$) (Table 2). When actigraphy data were analyzed, there were no significant differences found in total sleep time between the 2 groups.

Table 2 - Comparison of efficacy of 2 antipsychotic drugs on sleep quality in Iranian paradoxical insomnia patients.

Group	PSQI1 baseline mean	PSQI2 treatment mean	P-value	95% confidence interval
Olanzapine	11.8±2.3	2.6±1.6	<0.001	7.7-10.4
Risperidone	11.1±2.4	5±3.8	<0.001	-8.6-3.5
Olanzapine versus risperidone	0.50 (95% CI: -1.3-2.4)	-2.4 (95% CI: -4.8--0.1)	<0.04	

PSQI - Pittsburgh Sleep Quality Index, CI - confidence interval

Discussion. Our study on paradoxical insomnia treatment has 2 important findings. First, both olanzapine and risperidone were found to be short-term, efficacious treatments for paradoxical insomnia. Second, when the 2 treatments were directly compared, the treatment of paradoxical insomnia with olanzapine resulted in greater improvement of sleep quality as compared with risperidone.

Although, there are no reported studies to compare the efficacy of atypical antipsychotic drugs (especially olanzapine and risperidone) in treatment of paradoxical insomnia with other treatment protocols (including traditional antipsychotics, and benzodiazepines), our results are consistent with prior studies reporting the relationship between the improvement of sleep quality with the use of atypical antipsychotic drugs.¹³⁻²⁰ The results of this study suggest that atypical antipsychotic drugs may be considered as an effective insomnia treatment, specifically paradoxical insomnia. The results of this study may have several implications. First, in clinical practice, many of these patients often fail treatment with benzodiazepines that are often recommended as treatment for other forms of insomnia, resulting in lack of success and frustration by both the clinician and patient. On literature review, we were unable to find any published reports on the treatment outcome when using other insomnia treatment agents in these patients.

Second, an improvement was noted in the subjective complaint of sleep quality, which is the hallmark of paradoxical insomnia. Paradoxical insomnia patients have complaints that are not substantiated by results of objective measures such as polysomnography or actigraphy.⁸⁻¹¹ In fact, the treatment resulted in the patient's positive perception upon self reports that sleep quality improved, which may be considered the main goal of their treatment. Third, both olanzapine and risperidone were well tolerated during the 8-week study, and there were no reports of adverse side effects once the drugs were initiated. In our study, with careful assessment, these drugs were administered safely over the short-term. However, long-term follow-up of the patients for atypical antipsychotic drug side effects is necessary.²¹⁻²⁴ Prior studies have found that these drugs present with no risk of tolerance, psychomotor and cognitive impairment, anterograde amnesia, or rebound insomnia that is often reported with administration of some narcotic drugs.^{5,6} Future studies should both evaluate the safety and efficacy of these treatments over time.

It should be noted that the exact mechanism of atypical antipsychotic drugs (olanzapine and risperidone)

on paradoxical insomnia is not clear. It could be said that the involved mechanism in paradoxical insomnia is similar to one found in other types of insomnia that are treated by off-label use of atypical antipsychotics drugs.¹⁶⁻¹⁸ Alternatively, considering the probability that paradoxical insomnia may be a somatic delusion,¹² it may be possible that there is a mechanism involved that is similar to that found in other delusional disorders and in patients with schizophrenia and comorbid sleep difficulties. In these disorders that involve blocked D2 receptors, patients often respond to dopaminergic drugs.¹⁶⁻¹⁸ Further research is needed to better understand the mechanism involved in paradoxical insomnia and to investigate the mechanism responsible for improvement in the treatment with these atypical antipsychotic drugs.

Finally, we found a significant difference in the improvement in sleep quality based on which drug was administered. Olanzapine was more effective than risperidone ($p < 0.05$). Olanzapine is among the atypical antipsychotic drugs that have been reported to improve sleep quality in healthy volunteers and patients with mental health disorders. For example, olanzapine has been found to have a greater improvement on subjective quality of sleep when compared with other drugs such as risperidone and haloperidol. It is possible that this drug has a higher affinity to the H1 receptor, therefore having greater efficacy in improving sleep quality.¹⁴⁻¹⁹

This study investigated the treatment of paradoxical insomnia, which is a relatively understudied diagnosis to date. We found the use of either of the 2 atypical antipsychotics to be a safe and efficacious treatment for paradoxical insomnia in our study. However, our study did have limitations. First, this was not a double-blind protocol, and patients and prescribers were aware of the medication administered. Second, our study was 8 weeks in duration, and it is not clear if these medications have long-term consequences, such as rebound insomnia or tolerance.¹⁸⁻²¹ Similarly, although no adverse drug side effects (such as extra pyramidal and diabetes) were observed during intervention, long-term consequences remain unknown. Long-term, double blind placebo studies are needed. Third, we only directly compared the efficacy of 2 drugs. A comparison of their efficacy with non-medical treatments such as behavior therapy or the efficacy of a combination of the drugs with non-medical treatment is recommended. Finally, a lack of comparison of the PSQI1 and PSQI2 subscores limited further analysis of the results. This should be considered in future study.

In conclusion, atypical antipsychotic drugs, especially olanzapine, may be considered an appropriate

treatment for paradoxical insomnia. Treatment with atypical antipsychotic drugs resulted in improvement in self-reported insomnia in these participants, which is the overall goal of treatment in this population. However, physicians should monitor patients for adverse side effects that may be seen with its prescription over time. Further research is recommended to determine efficacy and safety of atypical antipsychotic drugs in insomnia treatment, particularly paradoxical insomnia, over time.

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