

## 기분장애에서 risperidone의 양면성\*

윤 도 준\*\*

### Risperidone as a Janus in Mood Disorder\*

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#### ABSTRACT

To examine the double-faced thymoleptic (antidepressant and antimanic) effects of risperidone in mood disorders, this article reviews the psychotropic-induced mania, thymoleptic effects of antipsychotics, therapeutic effects of risperidone and risperidone (RIS)-induced mania (RIM) in mood disorders, risk factors of RIM, possible neurochemical mechanism of these thymoleptic effects, pathophysiological and clinical significance of thymoleptic effects, and suggestive clinical guideline of RIS in mood disorders.

RIS appeared effective for bipolar disorder at a lower dose than that recommended for schizophrenia, especially in the cases of maintenance of mood stabilizers, and gradual titration from low doses. Manic induction/exacerbation can occur by chance during RIS treatment in mood disorders, schizoaffective disorders, and schizophrenias. The possible risk factors for RIM are refractory mood disorder, especially in bipolar I disorder with poor initial response; refractory schizoaffective disorders, especially in bipolar type with poor initial response; refractory chronic schizophrenias, especially with initial responses; psychotic features; higher initial doses; rapid titration; combined therapy with antidepressants in refractory depression; and RIS monotherapy in mania/hypomania.

RIS is a drug that preferentially block 5-HT<sub>2</sub> receptors. The effects of low dose are due mainly to the blockade of 5-HT<sub>2</sub> receptors. There are more gradual increase in D<sub>2</sub> blockade with increasing dose and this D<sub>2</sub> blocking properties become apparent at higher doses. This may be related to a modulation of dopaminergic transmission by 5-HT<sub>2</sub> antagonism at lower doses with the direct action of RIS on DA receptors coming into play at higher dose. The serotonergic antagonistic effect may be important for its effects on depressive symptoms. This, together with adequate blockade of D<sub>2</sub> receptors, may not necessarily lead to destabilization of mood disorder, but rather to more therapeutic effects. Therefore, this dose-receptor affinity relationship with both antidepressant and antimanic effects according to treatment duration can explain a continuum of antidepressant effect, antimanic effect, behavioral stimulation, and manic/hypomanic induction/exacerbation.

It was the recognition of a useful psychiatric side effects by a thoughtful observer with fertile minds that led to their ultimate utilization as psychotropic drugs, i.e., phenothiazine, MAOI, TCA, and lithium. And, in vivo pharmacological challenge by novel psychotropics, as a neurochemical probe, with more specific actions is a useful tool to select pharmacologically homogeneous subgroup of the same phenotypical (clinical) condition, to further study the unknown underlying pathogenesis of various mental illnesses.

Finally, RIS may be a useful alternative or adjunctive drug for patients with mood disorders without psychotic features or refractory to treatment with standard antipsychotic drugs. The more conservative doses (titrated slowly from 1 - 3 mg/d) of RIS, and maintenance of mood stabilizer in the cases with risk factors of RIM are recommended in mood disorder.

**KEY WORDS** : Risperidone · Mood disorder · Double-faced thymoleptic effects · Psychiatric side effect · Manic induction/exacerbation.

서론

risperidone 가 (Marder 1996).

eridone 가 (Stein 1997), (Songer Roaman 1996), (Lombroso 1995), (Di - 1996), (Purdon 1994), (Vanden Borre 1993), Lesch - Nyhan (Allen Rice 1996), (Tariot 1996), (Cook 1996), (Raheja 1995) (Sajatovic 1996b), (Madhusoodanan 1995; Zarate 1997), L - dopa (Meco 1994)

, risperidone ‘ risperidone (serotonin - dopamine antagonist, SDA) 가 (McElroy 1991), SDA risperidone (thymoleptic effect) 가 . Risperidone

(Hillert 1992). , (Goodnick 1995 ; Sajatovic 1996a) (mood stabilizer) ( 1995 ; McIntyre 1997 ; Small 1996 ; Tohen 1996 ; Vieta 1995) . (rapid cycling bipolar disorder) Vieta (1996) , clozapine (Keck 1995). risperidone Dwight (1994) risperidone (risperidone - induced mania) 가 . 가 .

(Schnierow Graeber 1996) (Barkin Pais 1997) . (Koek Kessler 1996) ( 1997 ; Byerly 1995 ; Diaz 1996 ; O' Croinin 1995 ; Schnierow Graeber 1996 ; Tomlinson 1996) , (Sajatovic 1996a ; Schaffer Schaffer 1996) (Barkin Pais 1997 ; Schnierow Graeber 1996) 가 . (McElroy 1996) ‘ risperidone , (psychiatric side effects) . Risperidone (ps - ychotropic drug) ( 1996), (antidepressant - associated mania) ( 1997a).

risperidone , risperidone , risperidone

항정신약물에 의한 조증 유발

(neuroleptic dys - phoria), , (supersensitivity psychosis) (cholinergic rebound), / , , lithium (?) ( 1996). 가 (Bauer 1994). ‘ ( )

가 . ( ) ( )  
 1 2 .1 )가 가  
 , 2 .  
 가 (McElroy 1996). Risperidone  
 가 (Ereshefsky Lacombe 1993)  
 가 risperidone  
 (Goodwin Jamison 1990). , ,  
 ( 1997 ;  
 가 가 (Stoll McElroy 1996).  
 1994). risperidone 가 .  
 가 (Altshuler 1995). ,  
 (antidepressant - induced mania)  
 ( ) (antidepr -  
 essant withdrawal mania) Mirin (1981) ,  
 Jones (1984) 가 risperidone  
 .  
 가 ( 1995), ne / risperido -  
 (Alan 1990 ; Sholomskas 1990), (Steiner 1991 ; port) / (case re -  
 Vieta 1992), ( 1995 ; risperidone (case series) .  
 1996) / .  
 , , 가  
 (affective spectrum 12 ( Table 1  
 disorder)(Bernstein 1995) ) 1 6 ( 4, [dys -  
 ) phoric mania] 2), 1 ,  
 2 , 3 ( 2, 1)  
 , 가 , risperidone  
 , ( 1 ), 가 .  
 ( 1 ), , ,  
 , ( ), 가 risperidone 4.5mg/d(  
 ( ), , , 2 10) 32.7 (  
 , TCA MAOI(RIMA ?) ( 10 60) ,  
 1997a).

**항정신병약물의 기분변화 효과**

(CGI>6). 4 ( 1 4) 3 가  
 risperidone  
 Clozapine risperidone SDA가 ' 3.6mg/d( 2 6), 120  
 . ( 60 180, 1 가 )  
 가 (CGI>6).  
 가 4.5mg/d(  
 1.5 6), 21 ( 14 28, 1  
 2 )  
 가 (Bernstein 1995). Clozapine 가 ,

(CGI>6). 12  
risperidone 6 , , ,  
3 , 2 , 1 , 1 가 ,  
가 1 (5 ) ,  
) (Table 1). 2 3mg/d ( 2 4) 10mg/d  
( ( 1)  
1 4) risperidone ( 3 18 ( Table 2 )  
9 (1 8, 1 2 1), 2 ,  
) ( 2, 3, 2)  
), 4.2mg/d( 1.9 6.5, 1  
), 19.9 ( 2 60)  
, (CGI>5) 79.6%  
4.5mg/d

**Table 1.** Case reports of successful risperidone therapy in mood/schizoaffective disorders

Pt	Age/Sex	Diagnosis	Medications(mg/d)/Duration of therapy(d)			Drug response		Ref
			RIS		Concurrent mood stabilizers & others	CGI	Latency to first efficacy(d)	
			max. dose	Titration pattern				
Mood disorder								
Bipolar disorder, manic								
1	34/F	Refractory bipolar I, manic with psychotic feature	10/21	G	D/D=lithium 900/30, haloperidol 10/30	7	2	1
2	23/M	Refractory bipolar I, manic with psychotic feature	3/10	S	D/B=lithium ??/?	7	few	1
3*	33/M	Refractory bipolar I, manic with psychotic feature	2/56	S		7	?	2
4*	44/M	Refractory bipolar I, manic with psychotic feature	2/28	S	D/D=valproate ??/? , haloperidol ??/?	6	?	2
5	43/F	Refractory bipolar I, dysphoric mania	8/21	G	M=lithium 1600/56, carbamazepine 800/56	6	soon	3
6	31/M	Refractory bipolar I, dysphoric mania	2/60	R	C=carbamazepine 1000/?	7	4	3
Depressive disorder								
7	?/M	Refractory recurrent major depression	3/60	G	M=MAOI phenelzine 60 - 75/?	7	2	4
8	31/F	Refractory comorbid dysthymia & borderline personality disorder	2/180	G	M=fluvoxamine 200 - 300/?	6	?	5
9	27/M	Refractory comorbid dysthymia & Pedophilia	6/?	G	M=fluoxetine 20 - 80/70	7	7	6
Schizoaffective disorder								
Schizoaffective disorder, bipolar type, manic								
1	40/M	Refractory schizoaffective disor, manic with psychotic feature	6/?	S	C=fluphenazine 20/?	6	?	2
2	67/F	Refractory schizoaffective disor, manic with psychotic feature & TD/senile dementia	1.5/14	G	M=lithium 1050/?	7	7	7
Schizoaffective disorder, depressed type								
3	69/F	Refractory schizoaffective disor, depressed with psychotic feature	6/28	R	M=lorazepam 4/?	7	?	8

RIS=risperidone, G=gradually increased, R=reduced dose, S=steady dose,  
\*Discontinued due to side effects except manic induction or exacerbation, TD=tardive dyskinesia  
D/D=discontinued during RIS therapy, D/B=discontinued when beginning RIS therapy  
M=maintained before & after beginning RIS therapy, C=combined when beginning RIS therapy  
CGI : 1=very much worse, 2=much worse, 3=worse, 4=unchanged, 5=mild improved, 6=much improved, 7=very much improved  
Ref. : 1. Goodnick(1995) ; 2. Sajatovic (1996a) ; 3. Vieta (1995) ; 4. Welner(1996) ; 5. Szigethy Schulz(1997) ; 6. Bourgeois Klein (1996) ; 7. Madhusoodanan (1995) ; 8. Benazzi(1996)

2.5 6.5), 12.5 ( 9.5 15.5)

(CGI>5) 100%

risperidone

4.2mg/d( 1.9 7, 2

), 6.8 ( 3 9.5, 2

) (CGI>5) 76%( 50 100, 1

1

1 risperidone

(Table 2).

**Table 2.** Case series of successful risperidone therapy in mood/schizoaffective disorder

Diagnosis	No. of all subjects	No. of CGI>5 cases(%)	Mean dose(mg/d)/ Duration of therapy(w)	Concurrent mood stabilizers	Ref.
Mood disorder					
Bipolar disorder, manic					
Bipolar I disor, manic	11	11(100)	6/8	C=lithium	1
Bipolar I disor, manic	30	30(100)	5.6/12	C=lithium, carbamazepine	2
Bipolar I disor, manic with psychotic feature	13	19( 92)	5.1/2	M=lithium, valproate, carbamazepine	3
Bipolar disorder, manic, depressed & mixed					
Refractory bipolar I disor, mixed with/ without psychotic feature	2	1( 50)	1.9/3	M=Ca antagonist, clonazepam	4
Bipolar I & II disor, mania/hypomania, mixed with/without psychotic feature	16	14( 88)	3.3/9	M=lithium, valproate, carbamazepine(n=12)	5
Refractory bipolar I(?) disor, 4 manic/hypomanic, 2 depressed	6	4( 67)	1 - 6*/60	M=lithium, car- bamazepine, valproate	6
Refractory bipolar I disor, 2 manic/hypomanic, 3 depressed, 4 mixed, 3 rapid cycling	12	4( 33)	2.75/24	M=lithium, valproate, carbamazepine	7
Refractory(n=9) bipolar I disor, 5 manic/hypomanic, 2 depressed, 6 mixed with 1 psychotic feature	14	12( 86)	2.8/6.4	M=lithium, valproate, carbamazepine, felbamate(n=11)	8
Bipolar I disor, 7 manic, 2 depressed, 2 mixed	11	11(100)	6.5/5	M=lithium, valproate, carbamazepine(n=11)	9
Depressive disorder					
Major depressive disor with psychotic feature	4	4(100)	2.5/15.5		5
Major depressive disor with psychotic feature	3	3(100)	6.5/9.5		9
Schizoaffective disorder					
Schizoaffective disorder, bipolar type					
Refractory schizoaffective disor, bipolar	3	2( 67)	1.9/3	M=lithium, Ca antagonist	4
Schizoaffective disor, bipolar	58	30( 52)	6.5/9.5	M=lithium, valproate, carbamazepine(n=41)	9
Schizoaffective disorder, type unspecified					
Refractory schizoaffective disor	4	2( 50)	6.1/6	M=valproate(n=3)	10
Refractory schizoaffective disor	14	NS	NS	NS	11
Schizoaffective disorder, depressive type					
Schizoaffective disor, depressive	2	2(100)	7/NS		12
Schizoaffective disor, depressive,	23	20( 87)	6.3/9.5		9
Schizoaffective disor, depressive	10	10(100)	2 - 10/6		13

NS=not specified. \*=maximal dose

C=combined when beginning RIS therapy. M=maintained before & after beginning RIS therapy

CGI : 1=very much worse, 2=much worse, 3=worse, 4=unchanged, 5=mild improved, 6=much improved, 7=very much improved  
 Ref. : 1. Small (1996) ; 2. (1995) ; 3. Tohen (1996) ; 4. Madhusoodanan (1995) ; 5. Jacobsen(1995) ; 6. McIntyre (1997) ;  
 7. Ghaemi Sachs(1996) ; 8. Ghaemi (1997) ; 9. Keck (1995) ; 10. Daniel (1996) ; 11. Negron (1996) ; 12. Dwight (1994) ; 13. Hil-  
 lert (1992)

# 정신질환에서 Risperidone에 의한 조증 유발 및 악화

Table 1

( 7 8) 가

## 1. 증례보고를 통한 정신질환에서 risperidone의 조증 유발/악화

가 가 .  
2 risperidone  
, risperidone  
3.2mg/d( 2.5 4)  
5.4mg/d(  
( 1997a), risperidone  
1.5 9) 85.7% (CGI>5) 가  
19 ( 1 43, 1 가 )  
risperidone  
6 7 2.3mg/d( 1.5 3)  
(behavioral stimulation, /  
(Table 3).  
Risperidone /  
15 ( Table 3 )  
7 , 6 ( 1 5, 1), 1 가 . 11, 가 4,  
2 ( ) 가 가  
가 71%  
가 risperidone 13 ( benzodiazepine 2,  
(Steiner 1991 ; Vieta 1992) risperidone 4, 3, 가 1,  
가 risperidone , 2, , benzodiazepine  
risperidone 1) 1 , , benzodiazepine  
benzodiazepine 1 ( ) .  
(5 ) 1 5.6mg/d( 11, 2, 1,  
2 8), 22 ( 3 60, 1 1 13 1  
) (4 ) (1 ) 2(Schinierow Graeber 1996)  
. 2 , 2 , 1 risperidone 6mg/d  
lithium rispe - 가 risperidone  
ridone 20% (CGI>5) . Table 1 risperidone  
risperidone ( 1 6) ' 2mg/d 3mg/d  
Table 1 ' 가 Table 1 ' ,  
(1 ) ' Table 3 3 2mg/d 가  
가  
1  
4mg/d, 8 Table 1

risperidone (1) ' 43%  
 가 가 '(CGI>5) Table 1  
 , Table 1 1 3 가  
 가 , Table 3 ' , Ta-  
 Table 1 가 ble 4 , Table 1  
 ri- Table 3

speridone  
 가  
 가 Table 3 2  
 risperidone ' D2/5-HT2 1 /  
 가 가

가 Table 1 1( (Schaffer Schaffer 1996).  
 1 ) 10mg/d ( ) 1  
 , Table 3 3( (Sajatovic 1996a). 가  
 1 ) 2mg/d ( ) ' - - / '가

가 ' ris- ( 3, 1, 2) 100% / 가  
 peridone / risperidone 7mg/d  
 가 (Dwight 1994)(Table 4).

가 / 3. 조증 유발 및 악화의 위험인자  
 Table 1-4 risperidone /  
 , Table 3 ' / , ' (

/ ( 100%, 1  
 100%, 71%) , ) 가  
 risperidone ' ) , ( 가  
 , 가 ) , ( ) , /

risperidone  
 ( 가 양면성 기분변화 효과의 기전

2. 증례시리즈를 통한 기분장애에서 risperidone에 의한 조  
 증 유발/악화의 유병율  
 Risperidone /

Medline 3 , 가 가  
 1 ( Table 4 가  
 ). ' 1 / , Risperidone  
 60% , (5HT2) 가 가  
 2.2mg/d(1 ) 가 /

**Table 3.** Case reports of risperidone-induced mania/manic exacerbation in mood disorders and all other mental disorders

Pt	Age / Sex	Diagnosis	Medications(mg/d)			Drug response		Ref
			RIS		Concurrent mood stabilizers & others	CGI	Manic induction or exacerbation Latency to onset(d)/ Duration of RIM (d)	
			max dose	Titration pattern				
Mood disorder								
Bipolar disorder, manic								
1	32/F	Refractory bipolar I disor, manic with psychotic feature	6	S	M=lithium, valproate	4	Manic exacerbation 3/1.5	1
2	47/M	Refractory bipolar I disor, manic with psychotic features	6	S	M=lithium, valproate	6*	Manic exacerbation ?/?	2
3	42/M	Refractory bipolar I disor, manic with psychotic feature	2	R		4	Manic exacerbation 3/?	3
4	52/M	Refractory bipolar I disor, manic with psychotic feature	8	S		4	Manic exacerbation 60/?	3
5	45/M	Refractory bipolar I disor, manic with psychotic feature	6	S	D/B=lithium, M=perphenazine	4	Behavioral stimulation** 21/?	3
Depressive disorder								
6	44/M	Refractory recurrent major depressive disor with psychotic feature	4	G	M=doxepine, alprazolam	4	Manic induction 8/3	4
Schizoaffective disorder								
Schizoaffective disorder, depressive								
1	29/M	Refractory schizoaffective disor, depressive with psychotic features	2.5	?	M=valproate	4	Manic induction ?/2	1
2	42/M	Refractory schizoaffective disor, depressive	4	S	D/B=lithium, perphenazine	4	Manic induction 2/14	2
Schizophrenia								
Refractory chronic schizophrenia								
1	46/M	Refractory chronic schizophr, acute exacerbation & TD	6	G	haloperidol	5***	Manic induction 21/60	5
2	31/F	Refractory chronic paranoid schizophr, acute exacerbation	6	G		4	Hypomanic induction 7/?	6
3	44/M	Refractory chronic disorganized schizophr, acute exacerbation	6	?		6	Manic induction ?/?	2
4	50/M	Refractory chronic schizophr, actue exacerbation & mild mental retardation	9	G		6***	Manic induction 40/39	7
5	57/F	Refractory chronic schizophr, acute exacerbation	6	G		6	Behavioral stimulation** 1/4	8
Chronic schizophrenia								
6	22/F	Chronic schizophr, acute exacerbation	1.5	S	alprazolam	5	Manic induction 2/?	9
7	29/M	Chronic paranoid schizophr, acute exacerbation	3	G		6	Hypomanic induction 43/5	9

RIS=risperidone, RIM=RIS induced mania/manic exacerbation, G=gradually increased, R=reduced dose, S=steady dose, D/B=discontinued when beginning RIS therapy. M=maintained before & after beginning RIS therapy, \*=improvement of psychotic symptoms, \*\*behavioral stimulation=anxiety, insomnia, restlessness. \*\*\*=improvement of negative symptoms. TD=tardive dyskinesia  
 CGI : 1=very much worse, 2=much worse, 3=worse, 4=unchanged, 5=mild improved, 6=much improved, 7=very much improved  
 Ref. : 1. Barkin Pais(1997) ; 2. Schnierow Graeber(1996) ; 3. Sajatovic (1996a) ; 4. Koek Kessler(1996) ; 5. Tomlinson(1996) ; 6. O'Croinin (1995) ; 7. Diaz(1996) ; 8. Byerly (1995) ; 9. (1997)



**Table 4.** Case series and prevalence of risperidone-induced mania/manic exacerbation in mood/schizoaffective disorder

No. of cases & prevalence (%)	No. of CGI>5 cases (%)	No. of all subjects	Mean dose (mg/d) /Duration of therapy	Concurrent mood stabilizers	Ref.
Risperidone-induced symptoms				Concurrent mood stabilizers	Ref.
Diagnosis at time of treatment					
Mood disorder					
6 (60)	5 (50)	10	0.5 - 1.0/?		1
Dose-related behavioral stimulation* in 3 of the 5 patients experienced a therapeutic effects Increase in hypomanic/manic symptoms in 3 of the 5 who did not experience a therapeutic response					
Refractory bipolar I(?) disorder, hypomanic/manic					
3 (60)	2 (40)	5	NS	NS	2
Manic exacerbation					
Refractory bipolar I disorder, manic					
3 (60)	2 (40)	5	3.8/3 d-3 m	D/D= valproate (n=1) D/B= lithium (n=1)	3
Manic exacerbation (n=2) Behavioral stimulation* (n=1)					
Refractory bipolar I disorder, manic					
Schizoaffective disorder					
6 (100)	3 (50) <sup>†</sup>	6	7/NS	M= lithium (n=1) C= valproate (n=1)	4
Switch of, or increase in, manic symptoms Schizoaffective disorder, bipolar (3 depressed <sup>†</sup> , 1 manic, 2 mixed)					

NS=not specified, \*behavioral stimulation=anxiety, insomnia, restlessness <sup>†</sup>schizoaffective disorder, bipolar type, depressed  
CGI : 1=very much worse, 2=much worse, 3=worse, 4=unchanged, 5=mild improved, 6=much improved, 7=very much improved  
D/D=discontinued during RIS therapy, D/B=discontinued when beginning RIS therapy, M=maintained before & after beginning RIS therapy. C=combined when beginning RIS therapy  
Ref. : 1. Schaffer (1996) ; 2. Negron (1996) ; 3. Sajatovic (1996a) ; 4. Dwight (1994)

(Ereshefsky Lacombe 1993).

D2/5HT2

risperidone

ridone

' risperidone

5HT2

'(Janssen 1988 ; Leysen 1988) , ' D2

5HT2

D2

가

가 ' (Janssen 1988 ; Ley-

sen 1994).

5HT2

가

(He Richardson 1995).

가

D2

25%

5HT2

60%,

25%

(Kinnon Li -

eberman 1996).

(6mg/d)

PET

가

D2

5HT2

가 80%, 90%

가 (permissive hypothesis of serotonin)

(Farde 1993).

가

가

(Good -

win Jamison 1990). , risperidone

(neurochemical probe)

(Diaz 1996).

lithium, valproate, carbamazepine

/ 10

### 양면성의 병태생리학적 및 임상적 의의

risperidone , 0.5 1.0mg/d

가 5 3 , 가

(activating effect) . 가

5 3 /

(Schaffer Schaffer 1996). , risperidone

D2/5-HT2 (5-HT2

speridone

D2 )

risperidone

, ris-

가 peridone

(1997b)

가

(mo-

(Bernstein 1995)

risperidone dified diagnosis - targeted psychopharmacology)( [

risperidone

] [ ] )

(5HT2) risperidone ( )

risperidone

(Meltzer Fatemi 1996).

Clozapine risperidone

, Table 1 3 'risperidone

가

가

(McElroy 1996). rispe-

ridone

/ 가

가

### 기분장애에서 Risperidone의 임상 치료 지침

(symptom - targeted psychopharmacology) ' 가

Risperidone (

( 1997b).

/ )가

SDA clozapine

risper-

idone

clozapine

(Ghaemi 1997).

4 8mg/d(Cohen LJ

( 1997b).

chlorpr- 1994)

omazine, MAOI, TCA, lithium, clozapine

(Ghaemi 1997), ' (1 3mg/d

( ) 가

/

가

benzodiazepine 가  
risperidone , ben -  
zodiazepine

감사의 글

risperidone

( )

중심 단어 : Risperidone

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