

# 기분장애의 병리와 치료에 있어 세로토닌의 역할

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## The Role of Serotonin in Pathology and Treatment of the Mood Disorders

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### ABSTRACT

The serotonin has been known to play important roles in pathology of the mood disorders. We summarize the evidences of serotonin in pathology of the mood disorders in a view of neuroanatomical and neurochemical aspects. Nowadays, the selective serotonin reuptake inhibitors(SSRIs) may be practically the first line of antidepressants with traditional tricyclic antidepressants(TCAs). Authors review the role of serotonin in the treatment of the mood disorders, in a view of the general considerations in selecting antidepressants, pharmacology, therapeutic indications, side effects, doses of medication, drug-discontinuation syndrome, drug-to-drug interactions, and special therapeutic situations.

**KEY WORDS** : Serotonin · Mood disorder · Selective serotonin reuptake inhibitor.

SSRIs

서 론

(serotonin)

기분장애의 병리

(subsystem)

가 가 , 2) , 3)

1)

가가

(Azmitia Whitaker - Azmitia 1991).

(Bloom Kupfer 1994).

20 가 가

(selective serotonin - reuptake inhibitors, SSRIs)가 가

(noradrenergic)

가 가

(raphe nucleus) (superior central nucleus)

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cortex), (rhinal cortex), (thalamus), (neo - pothalamus), (limbic system), (reticular formation), (locus ceruleus), (cerebellum) (sp -

inal cord)  
가

(serotonergic projections)  
(noradrenergic projection)  
(raphe nuclei)  
(locus ceruleus)

[<sup>3</sup>H]imipramine, [<sup>3</sup>H]paroxetine  
[<sup>3</sup>H]imipramine (bin -  
ding sites) 가  
[<sup>3</sup>H]imipramine  
(Leake 1991).  
(cortisol),

(Kaplan Sadock, 1995).

1) (tryptophan)  
, 2) 5 - HIAA(5 - hydroxy indoleacetic  
acid), 3) 5 - HT<sub>2</sub>  
가, 4) (transporter binding)  
, 5) , 6) fenfluramine  
(prolactin)  
(L - tryptophan)

가 fenfluramine  
(adrenocorticotrophic hormone),  
가  
fenfluramine  
가  
fenfluramine

(L - tryptophan/ )

amine  
가  
fenfluramine  
fenflur -  
amine  
가  
(Nash Meltzer 1991).

(Maes 1990).

SSRIs

5 - HIAA  
5 - HIAA  
5 - HIAA

가  
가  
Goodwin Jamison(1990)  
permissive hypothesis  
가 (catecholamine)

가

5 - HIAA (Reddy

1992).

5 - HT<sub>2</sub>  
, Sarrias (1987)  
5 - HT<sub>2</sub> 가 가

(activity)가  
(norepinephrine) (availability)가  
가

5 - HT<sub>2</sub> 가 가

### 기분장애의 치료

가  
5 - HT<sub>1</sub>, 5 - HT<sub>2</sub> 5 - HT<sub>3</sub> 3가  
5 - HT<sub>1</sub> 5 - HT<sub>1A</sub>, 5 -  
HT<sub>1B</sub>, 5 - HT<sub>1D</sub>, 5 - HT<sub>1E</sub> 5 - HT<sub>1F</sub>

(tricyclic antidepressants, TCAs)  
가

5 - HT<sub>1A</sub>가

가  
5 - HT<sub>1A</sub>  
(selective serotonin - reuptake inhibitors, SSRIs : fluoxetine )  
(serotonin - norepinep -

serotonin reuptake inhibitors, SNRIs : venlafaxine )  
 - (serotonin antagonist - reuptake in-  
 hibitors, SARIs : trazodone )

SSRIs  
 TCAs (concentration - dependent)

1. 항우울제 선택의 일반적 고려점

TCAs 30  
 SSRIs 10  
 fluoxetine, sertraline, paroxetine, fluvoxamine (Fig. 1). SSRIs

Burke 1992).  
 SSRIs P450

가  
 , SSRIs가  
 가 SSRIs  
 TCAs

SSRIs  
 , fluoxetine 2D6, 3A3/4 2C19  
 , sertraline 2C19 , paroxetine 2D6  
 (Schatzberg 1997c).  
 (acute tolerability index) TCAs

Shelton(1994)  
 'STEPS'  
 TCAs  
 SSRIs  
 (acute therapeutic index) 가  
 (narrower therapeutic index) (poorer tolerability)  
 (Preskorn 1995). TCAs

가 . SSRIs  
 (serotonin agonism)  
 (Kaplan Sadock 1995).  
 (late tolerability & safety issues)'  
 TCAs  
 ( )  
 ( )  
 ( )가 , TCAs

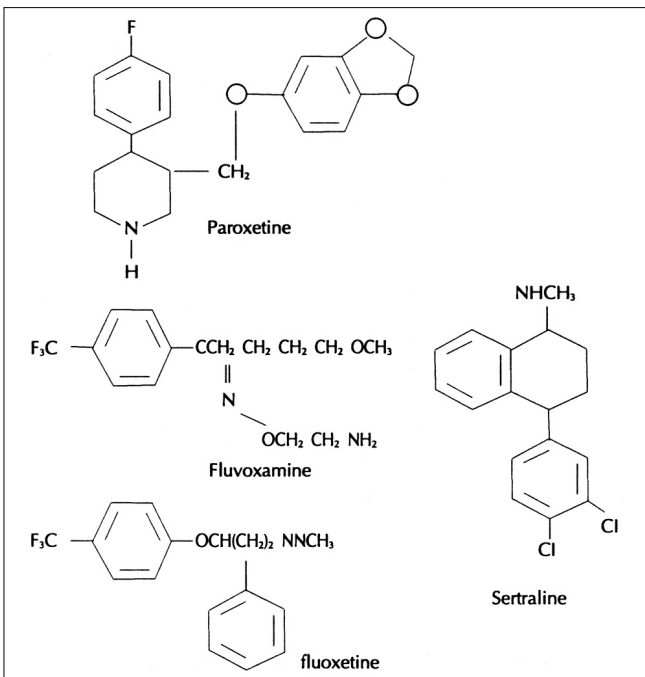


Fig. 1. Chemical structures of selective serotonin reuptake inhibitors.

Table 1. STEPS when considering the selection of an antidepressant

<b>Safety</b>	acute therapeutic index long-term safety pharmacokinetic interactions pharmacodynamic interactions
<b>Tolerability</b>	acute tolerability index late-emergent tolerability
<b>Efficacy</b>	overall efficacy unique spectrum of efficacy rate of onset of efficacy maintenance efficacy prophylactic efficacy
<b>Payment</b>	cost effectiveness
<b>Simplicity</b>	ease of optimum dosing need for dose titration need for divided daily dosing need for any specific monitoring

(Glassman 1993). SSRIs P450 가  
가 . alprazolam diazepam  
(Preskorn Magnus 1997).  
(pharmacokinetic interactions) ’  
. TCAs가  
가 , TCAs  
. Carbamazepine phenytoin TCAs ‘  
(inducer) ’ TCAs , fluoxetine pa-  
roxetine ‘ (inhibitor) ’  
가 (Preskorn 1993).  
‘ (pharmacodynamic interaction) ’  
, . TCAs  
, diphenylh-  
ydramine ,  
benztropine  
, 1 , prazosin  
quinidine  
membrane stabilization  
. SSRIs  
, 가 (monoamine oxidase in-  
hibitors, MAOIs)  
, (serotonin sy -  
ndrome) (Sternbach 1991).  
‘ (overall efficacy) ’  
, 가  
가 (Preskorn Bu -  
rke, 1992). TCAs  
, amitriptyline, desipramine, imipramine  
nortriptyline  
SSRIs - (flat do -  
se - respose curve)

(Tasman 1997).  
‘ (unique spectrum of efficacy) ’  
(atypical depression) TCAs MAOIs  
SSRIs가  
. 가  
TCAs가 SSRIs  
가 (Danish University Antidepressant Group 1990 ;  
Guelfi 1995).  
2. 생화학적 효과  
SSRIs , 2D6  
. Sertraline cytochrome p - 450 3A3/4 isoen-  
zyme . Fluoxetine sertraline  
가 . Fluoxetine( 36 )  
norfluoxetine(1 ) , sertraline(26 ) desmethy-  
lsertraline(64 ) hydroxyketone(100 ) ,  
가 fluoxetine  
sertraline parox-  
etine(20 ) fluvoxamine(15 ) (Table 2).  
SSRIs , paroxetine fluox-  
etine 가 .  
fluoxetine  
2 3 가 (Kalpan Sadock 1995).  
SSRIs . SSRIs  
가 (Schatzberg  
1997c).  
SSRIs  
Na/K adenosine triphosphatase(APTase)  
. TCAs  
가 , fluoxetine  
가 200  
. amitriptyline fluoxetine  
4 , 가 parox-  
etine 80 (Schat-  
zberg Nemeroff 1995).  
SSRIs  
가 , .

**Table 2.** Pharmacokinetics of selective serotonin reuptake inhibitors

SSRIs	Half-life(hours)	Metabolites & its half-life	Peak plasma level(hours)	% protein bound
Fluoxetine	24 - 72	norfluoxetine, 7 - 14 days	6 - 8	94
Sertraline	25	N-desmethyl-sertraline, 2 - 3 days	6 - 8	95
Paroxetine	20	N/A	2 - 8	99
Fluvoxamine	15	N/A	2 - 8	77

가 . (delayed effect) 가 (Fluoxetine Bulimia Nervosa Collaborative Study Group 1992).

가 SSRI 5-HT<sub>1</sub> 가 (Schatzberg 1987). fluoxetine 20mg/day 60mg/day 5mg/day (Beasley 1992a). Paroxetine (Bascara 1989). (Tulloch Johnson 1992, Reid 1994). (Sindrup 1990) (Langemark Oleson 1994) (Johnson 1992). Sertraline (Thompson 1992). (Jenike 1990). Fluvoxamine (Burton 1991).

3. 치료적 적응증 SSRI TCAs (Fig. 1).

가 4가 SSRI 가 가 SSRI 가 (intolerable) Fluoxetine 91%가 sertraline (tolerable) 가 (Brown Harrison, 1992). 가 SSRI (Sacchetti 1994). 가 (therapeutic indications) (Table 3) SSRI Fluoxetine (Cohn 1989, Beasley 1991b). Lithium 가 (Hellerstein 1993). 1500mg fluoxetine 234

4. 부작용 SSRI 가 TC As SSRI TCAs fluoxetine 가 가 SSRI 234

**Table 3.** Therapeutic indications among selective serotonin reuptake inhibitors

	Depression subtypes	Other disorders and/or symptoms
Fluoxetine	atypical depression, bipolar depression, dysthymia	bulimia nervosa, obsessive-compulsive disorder, panic disorder, borderline personality disorder, obesity, vomiting
Paroxetine	moderate or less severe depression in outpatients	panic disorder, obsessive-compulsive disorder, chronic pain, substance abuse
Sertraline	depression in outpatients, atypical depression, dysthymia	obsessive-compulsive disorder, social phobia, panic disorder & anticipatory anxiety
Fluvoxamine		obsessive-compulsive disorder

1992). SSRIs TCAs MAO-Is (Boyer Feighner fluoxetine fluoxetine sertraline paroxetine 가 가 가 SSRIs 가 (Stahl 1997). SSRIs trazodone (Table 4) . SSRIs 50 100mg zodone SSRIs tra- 1) 위장관계 부작용(gastrointestinal side effects) 가 SSRIs 가 (Schartzberg 1997c). , , , 가 3) 진정작용(sedation) (heartburn) 5-HT<sub>3</sub> fluoxet - paroxetine SSRIs ine 20 30% , 8 2 , 20mg/day . SSRIs ( 10 ) SSRIs 4 가 2 bromocriptine(2.5mg qid or bid) 가 4 가 4) 성기능부전(sexual dysfunction) SSRIs (delayed ejaculation, anorgasmia, impotence, diminished libido ) 4% , 5-HT<sub>3</sub> cisap - cisapride fluvoxam - 30% 50% 가 cytochrome P - 450 3A3/4 SSRIs (Jeffrey Winston 1995, Rothchild 1995). (Bergeron Biler 1994). 2) 중추신경계 활성화(CNS activation) , MAOIs cyprohep - 20 30% 가 , (jitteriness), tadine 4 12mg/day cyproheptadine SSRIs (Lipinski 1989). SSRIs가 (Jeffrey Wins -

**Table 4.** Common side effects of the selective serotonin reuptake inhibitors

Gastrointestinal	CNS activation	Neurological	Autonomic	Sexual dysfunction
Nausea	Insomnia	Headache	Excessive perspiration	Decreased libido
Dyspepsia	Jitteriness	Tremor		Delayed orgasm
Diarrhea	Agitation			
Emesis	Restlessness			
Cramping				

ton 1995). Bupropion bupropion SSRIs (Schatzberg Nemeroff 1995).  
가 가 (Walker 1991). Fluoxetine 20mg/day  
buspirone 5-HT<sub>1A</sub> partial agonist 15 30mg/day 80mg/day . fluo -  
yohimbine(5mg t.i.d) 가 가 xetine 20 40mg/day 가 . 60mg/  
(Jacobson 1992). 가 amantadine(100mg t.i.d.) day 20 40mg/day 가  
dopaminergic . Pa - 20mg/day 3  
roxetine sertraline , 가 40 80mg/day 가 .  
24 50% 10mg/day 80mg/day

fluoxetine 가 (Rothchild 1995). Paroxetine fluoxetine 가 20mg/day 20mg/day  
5) 자살사고 , 2 3  
Fluoxetine 6 가 20mg/day 2 3 .  
가 50mg/day 10 20mg  
, fluoxetine melancholia  
1991a). (Beasley fluoxetine Sertraline SSRIs 가  
, 가 traline 가 - ser -  
(Beasley 1992b, 50mg/day 가 SSRIs  
Wheadon 1992). fluoxetine (akathi - 가 SSRIs  
sia) 가 50mg/day . 3 4  
(Lipinski 1989). fluo - 50mg 200mg/day  
xetine 3 fluoxetine 50mg .  
, 3 Fluvoxamine 50  
propranolol 100mg/day 100mg/day  
(Rothchild Locke 1991). 100 200mg/day  
가 , 300mg/day가

6. 약물중단 증후군(drug-discontinuation syndrome)  
SSRIs  
6) 기 타 (withdrawal syndr -  
SSRIs (drug -  
seeking behavior) (discontinuation  
syndrome)  
1)  
(dose - dependent) 가 , 2)  
, propranolol(10mg t.i.d.) , ( ) ,  
paroxetine 20% , 3)  
, , 4)  
5. 용 량 , 5)  
SSRIs , 6)  
SSRIs TCAs MAOIs ine 가 fluoxet -  
가

(Scahtzberg 1997b).

SSRIs

(0.06 5.1%)

28%, paroxetine

50%

fluoxetine

(Ba -

가

rr 1995).

(Table 5)

(ataxia)

(disequilibrium),

7. 약물 상호작용

SSRIs

MAOIs, pentazocine nefazodone

(Table 6)

(Insel 1982).

lithium

carbamazepine

(Coupland 1996).

가

(down -

regulated)

SSRIs

가

-aminobutyric acid(GABA)

(Bel Artigas 1996).

(myoclonic jerking)

SSRIs MAOIs

SSRIs

. Paroxetine

MAOIs

(washout)

TCAs

(choli -

. Fluoxetine 5 6

nergic rebound)

(Dilsaver

fluoxetine

1987).

norfluoxetine 5

SSRIs

2

washout

fluoxetine

SSRIs 1

. MAOIs SS - RIs

2

가

가

. Cyprohe -

ptadine

dantrolene

SSRI

5 - HT<sub>2</sub>

, nefazodone

**Table 5.** Core somatic symptoms in SSRI discontinuation syndrome

	Examples
Disequilibrium	Dizziness Vertigo Ataxia
Gastrointestinal symptoms	Nausea Vomiting
Flu-like symptoms	Fatigue Lethargy Myalgia Chills
Sensory disturbances	Paresthesia Sensations of electric shock
Sleep disturbances	Insomnia Vivid dreams

**Table 6.** Psychological symptoms in SSRI discontinuation syndrome

	Examples
Core symptoms	Anxiety, agitation Crying spells Irritability
Minor symptoms	Overactivity Depersonalization Decreased concentration, slowed thinking Lowered mood Confusion Memory problems



가 . Nefazodone m - chlorphe -  
 nylpiperazine(m - CPP) 2D6 isoenzyme  
 SSRI nefazodone  
 ,  
 (dysphoric ag -  
 itation) m - CPP가 가  
 . Fluoxetine 4 5  
 SSRI nefazodone  
 nefazodone(50 100mg/day) SSRI  
 .  
 SSRIs cytochrome P -  
 450 SSRIs  
 (Table 7). SSRIs 2D6 isoenzyme  
 TCAs, 1C ,  
 SSRIs  
 가  
 fluoxetine TCAs TCAs  
 8 가 . Fluoxetine, paroxetine, sertraline  
 2D6 isoenzyme  
 2D6  
 SSRIs  
 , SSRIs TCA  
 가  
 2D6가 cytochrome P - 450 가  
 , 30가 . SSRIs  
 . Fluvoxamine the -  
 ophylline, caffeine, BZD haloperidol  
 1A2 isoenzyme  
 fluvoxamine theophylline  
 . Fluoxetine, paroxetine,  
 fluvoxamine 3A3/4 isoenzyme  
 . alprazolam, triazolam, trazodone  
 terfenadine, astemizole, triazalo  
 . alprazolam SSRIs  
 가 ,

가 .  
 8. 특수 상황에서의 치료

1) 노인 환자  
 .  
 가 . SSRIs  
 paroxetine sertraline

**Table 7.** Inhibition of cytochrome P-450 isoenzymes by antidepressants

Isoenzyme	Drug metabolized	Antidepressant inhibitors
2D6	tricyclic antidepressants	fluoxetine (norfluoxetine)
	bupropion	sertraline (desmethylsertraline)
	venlafaxine	paroxetine
	thioridazine	fluvoxamine (weakest)
	1C antiarrhythmics	
	-blockers	
	paroxetine	
	risperidone	
	codeine	
	haloperidol	
1A2	caffeine	fluvoxamine
	theophylline	
	phencetin	
	tricyclic antidepressants	
	clozapine	
3A3/4	alprazolam	fluoxetine
	triazolam	sertraline
	tricyclic antidepressants	fluvoxamine
	terfenadine	
	astemizole	
	carbamazepine	
	erythromycin	
	dexamethasone	
2C19	tricyclic antidepressants	fluoxetine
	warfarin	fluvoxamine
	tolbutamide	sertraline
	phenytoin	
	diazepam	

가 , fluoxetine  
 가 (Denchant Clissold 1991).

2) 심장기능의 이상이 있는 환자  
 SSRIs ,

가 , 가  
 fluoxetine (Leonard  
 Tollefson 1994).

3) 간기능의 이상이 있는 환자  
 SSRIs  
 (fluoxetine, sertraline, fluvoxamin), pl -  
 asma clearance (fluoxetine, paroxetine) total drug

exposure 가(fluvoxamine)

가 (Leonard Tollefson 1994).

가

SSRIs

TCAs

SSRIs

SSRI가

SSRIs

가

중심 단어 :

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