

기분장애의 치료에 있어서 약물의 Augmentation Strategies

정 영 인*†

Drug Augmentation Strategies in the Treatment of Mood Disorder

Young In Chung, M.D., Ph.D.*†

ABSTRACT

Mood disorder is a medical illness resulting from the disorder of CNS neurotransmission and its principal therapeutic tool is pharmacotherapy. Psychotherapeutic drugs for mood disorder have some clinical limitations which are due to no or partial response, decreased compliance for drug by the side effects, and delayed therapeutic effects. So, general hope of all clinicians that mood disorder will respond to a single psychotherapeutic agent may be the exception rather than the rule.

Recently, combined drug treatments have become increasingly popular to overcome the clinical limitations of individual agent in mood disorder. Combined treatments are usually used for augmenting or initiating rapidly the effect of drug, and for treating different target symptoms or drug side effects.

When combined treatments being tried, knowledge of the action mechanism, pharmacokinetics, and pharmacodynamics is crucial to cope with the possible adverse reactions of drugs.

KEY WORDS : Mood disorder · Combined drug treatment · Augmentation.

서 론

(Maas 1984 ; van Praag 1990).

가 (Bernstein 1995).

Lithium (Cade 1949)
 가 (monoamine oxidase inhibitor, MAOI) iproniazid (tricyclic antidepressant, TCA) imipramine (Keller Boland 1997). MAOIs TCAs, lithium TCAs
 가 가 , 가 가 Preskorn 1995), 35% (Burke 30 40% lithium (Bernstein 1995).

* Department of Psychiatry, Pusan National University Medical College & Pusan National University Hospital, Pusan, Korea

† : , 602 - 739 1가 10) (051) 240 - 7305,) (051) 248 - 3648

1980 serotonin selective reuptake inhibitor(SSRI) fluoxetine 가 bupropion(norepinephrine/dopamine reuptake inhibitor), venlafaxin(serotonin/norepinephrine reuptake inhibitor), nef-

azodone(serotonin - 2 antagonist/reuptake inhibitor), mirt - azapine(noradrenergic/specific serotonergic antidepressant), moclobemide(reversible inhibitor of MAO - A)

(Preskorn Burke 1992). , (target symptoms) lithium

가 MAOIs TCAs , TCAs bethanechol

(Quitkin Taylor 1996).

lithium

valproate carbamazepine

lithium

가

(mixed) (rapid cycling)

lithium

(Ballenger

양극성장애의 치료에 있어서 약물의 병합

1. 기분안정제(Mood stabilizer)간의 병합

Lithium

30 40% lithium

, lithium 40%

(Bernstein 1995 ; Chou 1991).

30 40%

20 30% lithium (Ge -

rshon Soares 1997). lithium

valproate carbamazepine

. Valproate carbamazepine

lithium

lithi -

um 가 (Ballenger Post

가 1980 ; Bowden 1995 ; Bowden McElroy 1995 ; Freeman

1992 ; Kishimoto 1983). Carbamazepine

(FDA)

valproate

lithium

(Bernstein 1995),

lithium

amazepine lithium

. Carb -

carbamazepine

lithium

가

가

, lithium

가 (DiCos -

tanzo Schifano 1991 ; Lipinski Pope 1982 ; McKeon

1992 ; Peselow 1994). Lithium carbamazepine

(Kramlinger Post 1990)

(sinus node)

(Steckler 1994)

병합약물요법의 목적

(monopharmacy)

가

가

가

가

가

가

가

가

(neurotoxicity) 가
 가 Lithium valproate
 , Lithium carba-
 mazepine
 가 가 (McElroy 1988 ; Shar-
 ma Persad 1992 ; Sharma 1988).
 Lithium 가 valproate ca-
 rbamazepine
 carbamazepine

2. 기분안정제와 항정신병약물의 병합

Lithium
 가 lithium
 lithium
 (Garfinkel 1980 ; Johnson 1971), halop-
 eridol 가
 (Bernstein 1995).

가 (Chou 1991), li-
 thium
 (Biederman
 1979 ; Garfinkel 1980).
 Lithium
 가
 lithium 가
 가 (Bernstein
 1995).

Elroy 1991),
 1994 ; Suppes 1994). Clozapine risperid-
 one 가 (Goodnick 1995 ;
 Hillert 1992 ; Sajatovic 1996)
 (Keck 1995). risperidone

valproate , lithium

Carbamazepine
 carbamazepine

3. 기분안정제와 benzodiazepine의 병합

Benzodiazepine 가 clonaze-
 pam 가 (Chouinard 1983 ;
 Victor 1984)
 benzodiazepine
 clonazepam lorazepam
 (Bradwejn 1990).

benzodiazepine
 lithium

lithium benzodiazepine
 clonazepam
 (Bernstein 1995).
 Lithium benzodiazepine
 clonazepam lorazepam ,
 clonazepam 1
 6mg lorazepam 1.5 8mg

4. 기분안정제와 감상선호르몬의 병합

(su-
 bclinical) 가 가 (Wh-
 ybrow 1992). lithium

(Kimmel
 Goodwin 1979 ; Wehr 1988), TCAs
 MAOIs SSRIs,
 Bupropion 가 가
 bupropion SSRIs
 가 가

가

TCAs

5. 기분안정제와 기타 약물의 병합

Clonidine

valproate

가

(Schatzberg 1996).

thium

가

clonidine li -

(Hardy 1986).

2. 항우울제와 호르몬의 병합

Clonidine

가

triiodothyronine(T₃)

TCAs

TCAs

, T₃

가

Ca⁺⁺

가

lithium

TCAs

T₃ aug -

(Dubovsky 1993 ; Giannini 1987).

mentation lithium

(Joffe

Ca⁺⁺

verapamil, nifedipine, nim -

1993). Thyroxine(T₄) T₃

가

odifine

diltiazem

. Ca⁺⁺

T₃ MAOIs

TCAs

verapamil nifedipine

, MAOIs

주요우울장애의 치료에 있어서 약물의 병합

lithium

T₃ SSRIs

(Crowe 1990 ; Gupta 1991 ; Joffe 1992).

1. 항우울제와 기분안정제의 병합

T₃

T₃

TRH

TCAs

lithium augmentation

TSH

가

(Targum

가

. Lithium

가

1984).

(Goodwin 1972 ; Souza Goodwin 1991),

T₃

1

(Go -

(De Montigny 1981 ;

odwin 1982) 2

. T₃

Nelson Majore 1986).

TCAs

lithium

25 µg

1

50 µg

augmentation

65%

(Keller Boland

,

3

(APA 1993).

1997). TCAs

lit -

T₃ 60

3

12.5 µg

hium

72

T₃

(De Montigny 1981),

3

T₃

. TCAs MAOIs SSRIs, bupropion

lithium

가

(Apter 1991 ; Dinan 1993 ; Pope

estrogen

1988 ; Price 1985).

Lithium

가

estrogen

가

600mg

(Sherwin 1991),

hium

lit -

estrogen

가

(Sichel 1995).

0.8 mEq/L가

0.5

Estrogen

가

TCAs

0.8 1.2mEq/L

(Phillips Ni -

가

estrogen

erenberg 1994). Lithium

3

6

estrogen

estrogen

5 25mg

Carbamazepine

가 , lithium

3. 항우울제와 정신자극제(Psychostimulant)의 병합

(Folks 1982). Carbamazepine TCAs

1960

cocaine

carbamazepine

TCAs

amphetamines

- in refractory depression. *Ann Clin Psychiatry* 2 : 7-10
- Artigas F, Perez V, Alvarez E (1994)** : Pindolol induces a rigid improvement of depressed patient treated with serotonin reuptake inhibitors. *Arch Gen Psychiatry* 51 : 248-251
- Ballenger JC, Post RM (1980)** : Carbamazepine (Tegretol) in manic-depressive illness : A new treatment. *Am J Psychiatry* 137 : 782-790
- Bernstein JG (1995)** : Handbook of drug therapy in psychiatry. 3rd ed, St. Louis, Mosby, pp 112-152
- Biederman J, Lerner Y, Belmaker RH (1979)** : Combination of lithium carbonate and haloperidol in schizoaffective disorder. *Arch Gen Psychiatry* 36 : 327-333
- Blier P, Bergeson R (1995)** : Effectiveness of pindolol with selected antidepressant drug in the treatment of major depression. *J Clin Psychopharmacol* 15 : 217-222
- Bowden CL (1995)** : Predictors of response to divalproex and lithium. *J Clin psychiatry* 3 : 25-30
- Bowden CL, McElroy SL (1995)** : History of the development of valproate for treatment of bipolar disorder. *J Clin Psychiatry* 3 : 3-5
- Bradwejn J, Shriqui C, Koszycki D, Meterissian G (1990)** : Double-blind comparison of the effects of clonazepam and lorazepam in acute mania. *J Clin Psychopharmacol* 10 : 403-408
- Burke MJ, Preskorn SH (1995)** : Short-term treatment of mood disorders with standard antidepressants, In : *Psychopharmacology, Vol 2*. Ed by Bloom FE, Kupfer DJ, New York, Raven Press, pp 1053-1065
- Cade JFJ (1949)** : Lithium salts in the treatment of psychotic excitement. *Med J Aust* 2 : 349-352
- Chiarello RJ, Cole JO (1987)** : The use of psychostimulants in general psychiatry. *Arch Gen Psychiatry* 44 : 286-295
- Chou JCY (1991)** : Recent advances in treatment of acute mania. *J Clin Psychopharmacol* 11 : 3-21
- Chouinard G, Young SN, Annable L (1983)** : Antimanic effects of clonazepam. *Biol Psychiatry* 18 : 451-466
- Crowe D, Collins JP, Rosse RB (1990)** : Thyroid hormone supplementation of fluoxetine treatment. *J Clin Psychopharmacol* 10 : 150-151
- De Montigny C, Grunberg F, Mayer A, Deschenes JP (1981)** : Lithium induces rapid relief of depression in tricyclic antidepressant drug non-responders. *Br J Psychiatry* 138 : 252-255
- Di Costanzo E, Schifano F (1991)** : Lithium alone or in combination with carbamazepine for the treatment of rapid-cycling bipolar affective disorder. *Acta Psychiatr Scand* 83 : 456-459
- Dinan T (1993)** : Lithium augmentation in sertraline-resistant depression : A preliminary dose response study. *Acta Psychiatr Scand* 88 : 300-301
- Dubovsky SL (1993)** : Calcium antagonists in manic-depressive illness. *Neuropsychobiology* 27 : 184-192
- Fawcett J, Kravitz HM, Zajecka JM, Schaff MR (1991)** : CNS stimulant potentiation of monoamine oxidase inhibitors in treatment refractory depression. *J Clin Psychopharmacol* 11 : 127-132
- Folks DG (1980)** : Carbamazepine treatment of selected affectively disordered inpatients. *Am J Psychiatry* 139 : 115-117
- Freeman TW, Clothier JL, Pazzaglia P, Lesem MD, Swann AC (1992)** : A double-blind comparison of valproate and lithium in the treatment of acute mania. *Am J Psychiatry* 149 : 108-111
- Garfinkel PE, Stancer HC, Persad E (1980)** : A comparison of haloperidol, lithium carbonate, and their combination in the treatment of mania. *J Affect Disord* 2 : 270-288
- Gershon S, Soares JC (1997)** : Current therapeutic profile of lithium. *Arch Gen Psychiatry* 54 (1) : 16-20
- Giannini AJ, Taraszewski R, Loisselle RH (1987)** : Verapamil and lithium in maintenance therapy of manic patients. *J Clin Pharmacol* 27 : 980-982
- Goodnick (1995)** : Risperidone treatment of refractory acute mania. *J Clin Psychiatry* 56 : 431-432
- Goodwin FK, Murphy DL, Dunner DL (1972)** : Lithium response in unipolar versus bipolar depression. *Am J Psychiatry* 129 : 44-47
- Goodwin FK, Prange A, Post R, Muscettola G, Lipton M (1982)** : Potentiation of antidepressant effects by L-triiodothyronine in tricyclic nonresponders. *Am J Psychiatry* 139 : 34-38
- Gupta S, Masand P, Tanquary JF (1991)** : Thyroid hormone supplementation of fluoxetine in the treatment of major depression. *Br J Psychiatry* 159 : 866-867
- Hardy MC, Lecrubier Y, Widlocher D (1986)** : Efficacy of clonidine in 24 patients with acute mania. *Am J Psychiatry* 143 : 1450-1453
- Hillert A, Maier W, Wetzel H, Benkert O (1992)** : Risperidone in the treatment of disorders with a combined psychotic and depressive syndrome : A functional approach. *Pharmacopsychiatry* 25 : 213-217
- Hollander E, DeCaria CM, Schneier FR, Schneier HA, Liebowitz MR, Klein DF (1990)** : Fenfluramine augmentation of serotonin reuptake blockade antiobsessional treatment. *J Clin Psychiatry* 51 : 119-123
- Joffe RT (1992)** : Triiodothyronine potentiation of fluoxetine in depressed patients. *Can J Psychiatry* 37 : 48-50
- Joffe RT, Levitt AJ, Bagby RM, MacDonald C, Singer W (1993)** : Predictors of response to lithium and triiodothyronine augmentation of antidepressants in tricyclic non-responders. *Br J Psychiatry* 163 : 574-578
- Joffe RT, Schuller DR (1993)** : An open study of buspirone augmentation of serotonin reuptake inhibitors. *J Clin Psychiatry* 54 : 269-271
- Johnson G, Gershon S, Burdock EI, Floyd A, Hekimian L (1971)** : Comparative effects of lithium and chlorpromazine in the treatment of acute manic states. *Br J Psychiatry* 119 : 267-276
- Keck PE, Wilson DR, Strakowski SM, McElroy SL, Kizer DL, Balistreri TM, Holtman HM, DePriest M (1995)** : Clinical predictors of acute risperidone response in schizophrenia, schizoaffective disorder, and psychotic mood disorders. *J Clin Psychiatry* 56 : 466-470
- Keller MB, Boland RJ (1997)** : Antidepressants, In : *Psychiatry, Vol 2*. Ed by Tasman A, Kay J, Lieberman JA, Philadelphia, WB Saunders, pp 1606-1639
- Kimmel SE, Calabrese JR, Woynshville MJ, Meltzer HY (1994)** : Clozapine in treatment-refractory mood disorders. *J Clin Psychiatry* 55 : 91-93
- Kishimoto A, Ogura C, Hazama H, Inoue K (1983)** : Long-term prophylactic effects of carbamazepine in affective disorder. *Br J Psychiatry* 143 : 327-331
- Kramlinger KG, Post RM (1990)** : Addition of lithium carbonate to carbamazepine : hematologic and thyroid effects. *Am J Psychiatry* 147 : 615-620

- Lipinski JF, Pope HG Jr (1982)** : Possible synergistic action between carbamazepine and lithium carbonate in the treatment of three acutely manic patients. *Am J Psychiatry* 139 : 948-949
- Mass JW, Koslow SH, Katz MM, Bowden CL, Gibbons RL, Stokes PE, Robins E, Davis JM (1984)** : Pretreatment neurotransmitter levels and response to tricyclic antidepressant drugs. *Am J Psychiatry* 141 : 1159-1171
- McElroy SL, Dessain EC, Pope HG, Cole JO, Keck PE, Frankenberg FR, Aizley HG, Obien S (1991)** : Clozapine in the treatment of psychotic mood disorders, schizoaffective disorder, and schizophrenia. *J Clin Psychiatry* 52 : 411-414
- McElroy SL, Keck PE, Pope HG, Hudson JI (1988)** : Valproate in the treatment of rapid-cycling bipolar disorder. *J Clin Psychopharmacol* 8 : 275-279
- McKeon P, Manley P, Swanwick G (1992)** : Manic-depressive illness : II. Treatment outcome and bipolar disorder subtypes. *Ir J Psychol Med* 9 : 9-12
- Nelson JC, Majore CM (1986)** : Lithium augmentation in psychotic depression refractory to combined drug treatment. *Am J Psychiatry* 143 : 363-366
- Nierenberg AA, Cole JO, Glass L (1992)** : Possible trazodone potentiation of fluoxetine : a case series. *J Clin Psychiatry* 53 : 83-85
- Peselow ED, Fieve RR, Difiglia C, Sanfilippo MP (1994)** : Lithium prophylaxis of bipolar illness : The value of combination treatment. *Br J Psychiatry* 164 : 208-214
- Phillips KA, Nierenberg AA (1994)** : The assessment and treatment of refractory depression. *J Clin Psychiatry* 55 (suppl) : 20-26
- Pope HG Jr, McElroy SL, Nixon RA (1988)** : Possible synergism between fluoxetine and lithium in refractory depression. *Am J Psychiatry* 145 : 1292-1294
- Preskom SH, Burke M (1992)** : Somatic therapy for major depressive disorder : Selection of an antidepressant. *J Clin Psychiatry* 53 (suppl) : 5-18
- Price LH, Charry DS, Heninger GR (1985)** : Efficacy of lithium-tranlylcypromine treatment in refractory depression. *Am J Psychiatry* 142 : 619-623
- Quitkin FM, Taylor BP (1996)** : Antidepressants, In : *Current psychotherapeutic drugs*, 1st ed, Ed by Klein DF, Rowland LP, New York, Brunner/Mazel, pp23-28
- Rothschild AJ, Samson JA, Bessette MP, Carter-Campbell JT (1993)** : Efficacy of the combination of fluoxetine and perphenazine in the treatment of psychotic depression. *J Clin Psychiatry* 54 : 338-342
- Sajatovic M, DiGiovanni SK, Bastani B, Hattab H, Ramirez LF (1996)** : Risperidone therapy in treatment refractory acute bipolar and schizoaffective mania. *Psychopharmacol Bull* 32 : 55-61
- Schatzberg AF, DeBattista CB, DeGolia S (1996)** : Valproate in the treatment of agitation associated with depression. *Psychiatric Annals* 26 : 1-4
- Seth R, Jennings AL, Bindman J, Phillips J, Bergmann K (1992)** : Combination treatment with noradrenaline and serotonin reuptake inhibitors in resistant depression. *Br J Psychiatry* 161 : 562-565
- Sharma V, Persad E (1992)** : Augmentation of valproate with lithium in a case rapid cycling affective disorder. *Can J Psychiatry* 37 : 584-585
- Sharma V, Persad E, Mazmanian D, Karunaratne K (1993)** : Treatment of rapid cycling bipolar disorder with combination therapy of valproate and lithium. *Can J Psychiatry* 38 : 137-139
- Sherwin BB (1991)** : Estrogen in refractory depression, In : *Advances in Neuropsychiatry and Psychopharmacology*, Vol 2. Ed by Amsterdam JD, New York, Raven Press, pp209-218
- Sichel DA, Cohen LS, Robertson LM, Ruttenberg A, Rosenbaum JF (1995)** : Prophylactic estrogen in recurrent postpartum affective disorder. *Biol Psychiatry* 38 : 814-818
- Souza FGM, Goodwin GM (1991)** : Lithium treatment and prophylaxis in unipolar depression : A meta-analysis. *Br J Psychiatry* 158 : 666-675
- Steckler TL (1994)** : Lithium-and carbamazepine-associated sinus node dysfunction : nine year experience in a psychiatric hospital. *J Clin Psychopharmacol* 14 : 336-339
- Stern SI, Mendels J (1981)** : Drug combinations in the treatment of refractory depression : a review. *J Clin Psychiatry* 42 : 368-373
- Suppes T, Phillips KA, Judd CR (1994)** : Clozapine treatment of nonpsychotic rapid cycling bipolar disorder : A report of three cases. *Biol Psychiatry* 36 : 338-340
- Targum SD, Greenberg RD, Harmon RL, Kessler K, Salerian AJ, Fram DH (1984)** : Thyroid hormone and the TRH stimulation test in refractory depression. *J Clin Psychiatry* 45 : 345-346
- van Praag HM, Asnis GM, Kahn RS, Brown SL, Korn M, Friedman JMH, Wetzlers (1990)** : Monoamines and abnormal behavior : A multiaminergic perspective. *Br J Psychiatry* 157 : 723-734
- Victor BS, Link NA, Binder RL, Bell IR (1984)** : Use of clonazepam in mania and schizoaffective disorders. *Am J Psychiatry* 141 : 1111-1112
- Wehr TA, Goodwin FK (1979)** : Rapid cycling in manic-depressives induced by tricyclic antidepressants. *Arch Gen Psychiatry* 36 : 555-559
- Wehr TA, Sack DA, Rosenthal NE, Cowdry RW (1988)** : Rapid cycling affective disorder : contributing factors and treatment responses in 51 patients. *Am J Psychiatry* 145 : 179-184
- Whybrow PC, Bauer MS, Gyulai L (1992)** : Thyroid axis considerations in patients with rapid cycling affective disorder. *Clin Neuropharmacol* 15 : 391A-392A