

Combining antidepressants: is there any evidence?

Graylands Hospital Drug Bulletin 2003 Vol 11 No.1 February ISSN 1323-1251

Many patients with depression have an inadequate response to antidepressant monotherapy. Up to 20% of patients may remain chronically depressed, even after multiple interventions⁽¹⁾. Despite the lack of evidence, combinations of antidepressants are increasingly being used to treat refractory cases.

General principles of combination

The typical rationale behind combination strategies is to broaden the effect on the CNS by combining agents that act on different neurotransmitter systems. There are three main ways to increase neurotransmission:

- ❖ Increase serotonergic action eg. using SSRIs
- ❖ Increase noradrenergic action eg. using reboxetine
- ❖ Use drugs that boost both serotonin & noradrenaline even as single agents - so called "heroic strategy" eg. venlafaxine, mirtazapine.

For how long should the combination be maintained?

A recent review⁽²⁾ suggested that improvement following antidepressant combination occurs within approximately 4-6 weeks, so it is worthwhile waiting this period of time to assess patient response. Most studies focused on the short-term outcome and little is known as to the recommended duration for treatment with the combination. The author suggests that the combination be maintained for 6 to 9 months after remission is obtained and then an attempt be made to gradually discontinue one of the two antidepressants.

The table overleaf summarises the evidence, where available, for different combinations and comments on the tolerability/safety of each. Information has been sourced from various psychotropic texts and journals (mostly from a recent review article).

Bupropion is mentioned in the literature as a possible agent for augmentation. It has not been included in the table as it is not licensed for treatment of depression in Australia.

Advantages and Disadvantages of Combination Strategies

ADVANTAGES	DISADVANTAGES
❖ Builds on partial response; patient not demoralised at "starting again"	❖ Polypharmacy and increased potential for drug interactions
❖ More rapid onset of antidepressant effects	❖ Reduced compliance
❖ May reduce side effects induced by first drug	❖ Increased adverse effects
❖ No discontinuation symptoms	❖ Additional cost

Combination	Recommendation?	Evidence?	Author	N	Drug & Dose mg/day
TCA ∪ MAOI	Possible benefit – patient monitoring important. See opposite.	Open trials RCT Case series	Amsterdam 1997 ⁽³⁾ Berlanga 1995 ⁽⁴⁾ Sethna 1974 ⁽⁵⁾ Davidson 1978 ⁽⁶⁾ Schmauss 1988 ⁽⁷⁾	27 25 12 17 94	CMI/DMI/AMI/IMI: 25-300, NTP 100-300, TD of MAOI ISO: 28 (m), AMI 132 (m) PHE: 45, AMI: 75 AMI: 71(m), PHE: 34(m) TCP: 13(m), TD of TCA
SSRI ∪ MAOI	Not recommended – associated risks.	N/A	N/A	-	N/A
SSRI ∪ RIMA	Caution – fatalities reported in literature.	Open trials	Joffe 1994 ⁽¹⁰⁾ Hawley 1996 ⁽¹¹⁾	11 19	MOC:452(m),SRT:125(m),FLV:130(m) MOC: 150-600, FLU/PXT: 20
SSRI ∪ TCA	Possible benefit – combination for which most evidence available. Patient monitoring important.	Open trials RCT Case series	Amsterdam 1997 ⁽³⁾ Levitt 1999 ⁽¹²⁾ Weilburg 1991 ⁽¹³⁾ Zajacka 1995 ⁽¹⁴⁾ Fava 1994 ⁽¹⁵⁾ Seth 1992 ⁽¹⁶⁾ Weilburg 1989 ⁽¹⁷⁾ Nierenberg 1992 ⁽¹⁸⁾	27 13 20 25 41 8 30 8	As above, TD of FLU DMI/IMI: 70(m), FLU: 44 (m) DMI/NTP: 10-50, FLU: 20-40 HCA:113 (m), FLU: 73 (m) FLU: 40-60, DMI: 25-50 NTP 25-75, SRT: 50-100 IMI equivalents 0-250, FLU 20-60 FLU: 32(m), TRZ 97 (m)
SSRI ∪ SSRI	Limited evidence.	Open trial Case reports	Bondolfi 1996 ⁽¹⁹⁾ Hunchak 1997 ⁽²⁰⁾	7 6	CIT: 40, FLV 50-100 Various SSRIs at TD
SSRI/Venlafaxine ∪ Mirtazapine	Possible benefit. Venlafaxine/mirtazapine combo is theoretically most powerful but no supporting evidence	Open trial RCTs	Carpenter 1999 ⁽²¹⁾ Carpenter 2002 ⁽²²⁾ Debonnel 2000 ⁽²³⁾	20 26 60	MIR: 15-30, TD of SSRI/VEN MIR: 15-30, TD of SSRI/VEN, PXT: 20-30, MIR 30-45
SSRI ∪ Reboxetine	Theoretical potential – limited evidence.	Case reports	Lucca 2000 ⁽²⁴⁾ Devarajan 2000 ⁽²⁵⁾	14 4	REB: 2-4, TD of SSRI REB: 4-6, CIT: 20-60
SSRI ∪ Venlafaxine	Only anecdotal evidence available.	Anecdotal reports ⁽²⁾	N/A	-	N/A
TCA ∪ Venlafaxine	Limited evidence.	Open trial	Gomez 2000 ⁽²⁹⁾	11	IMI:217(m), CMI:202(m),VEN:192 (m)
SSRI ∪ Nefazodone	Only anecdotal evidence available.	Anecdotal reports ⁽²⁾	N/A	-	N/A

COMBINATION KEY: TCA=tricyclic antidepressant, MAOI=monoamine oxidase inhibitor (phenelzine, tranylcypromine), SS=serotonin syndrome, RIMA=reversible inhibitor of monoamine oxidase A (moclobemide), SSRI=selective serotonin reuptake inhibitor

DRUG KEY: CIT=citalopram, CMI=clomipramine, DMI=desipramine, FLU=fluoxetine, FLV=fluvoxamine, HCA=heterocyclic antidepressant, IMI=imipramine, ISO=isocarboxid, m=mean, MIR=mirtazapine, MOC=moclobemide, NTP=nortriptyline, PHE=phenelzine, PXT=paroxetine, REB=reboxetine, SRT=sertraline, TCP=tranylcypromine, TD=therapeutic dose, TRZ=trazodone, VEN=venlafaxine; N/A=not applicable

Therapeutic Points to Consider with Combination

- ❖ Old-fashioned strategy, fallen out of favour over the years.
 - ❖ Potential dangers are sudden hypertensive episodes, delirium, seizures, drug and dietary interactions and obesity.
 - ❖ Most problems occur when TCA added to pre-existing MAOI; fewer adverse events have been reported with the reverse ⁽⁸⁾.
 - ❖ Preferably separate doses i.e. MAOI in morning, TCA at night.
 - ❖ Add one to another in low dose and build up slowly **OR** stop all antidepressants, wait a week, then start both together at low dose and build up again (latter seems to be most widely favoured strategy)⁽⁸⁾.
 - ❖ ?Avoid clomipramine (serotonergic side effects may be intolerable)⁽¹⁾.
-
- ❖ Combination associated with SS; number of confirmed fatalities ⁽⁹⁾.
 - ❖ Risk outweighs any potential benefit.
-
- ❖ Same potential for SS but less problematic than MAOI/SSRI combination.
 - ❖ Insomnia may be troublesome adverse effect.
 - ❖ Overdoses with moclobemide and SSRIs can be dangerous; number of completed suicides with intentional overdoses of this combination reported in the literature ⁽⁹⁾.
-
- ❖ Possible increased rapid onset of action (?due to accelerated receptor down-regulation) ⁽²⁾.
 - ❖ Main problem with this combination is potential for elevated TCA plasma levels due to inhibition of metabolism via the cytochrome P450 system. Such interactions may give rise to intolerable adverse effects; cardiac toxicity is of concern.
 - ❖ ?Avoid strong 2D6 inhibitors*. Citalopram may be safest SSRI to use.
 - ❖ Monitor TCA plasma levels and use low dose TCA i.e. 25-75mg. Avoid clomipramine (see above).
-
- ❖ Increased intensity of serotonergic side effects and theoretical risk of developing SS.
 - ❖ High potential for drug-drug interactions.
-
- ❖ Doses of 15-30mg mirtazapine at night quoted as “add-on” therapy.
 - ❖ Limited part played by CYP450 system in mirtazapine metabolism so reduced potential for drug-drug interaction.
 - ❖ May help with SSRI-induced sexual dysfunction.
 - ❖ Potential for weight gain associated with combination.
-
- ❖ Reboxetine is favoured noradrenergic agent for combination over TCAs due to reduced potential for drug interaction and better tolerability. ?Avoid fluvoxamine due to potent CYP3A4 inhibition.
 - ❖ Drug interaction study suggested safety of fluoxetine/reboxetine combination ⁽²⁶⁾.
-
- ❖ Doses of 75-300mg venlafaxine used in SSRI non-responders ⁽²⁾.
 - ❖ SSRI inhibition of metabolism may lead to elevated venlafaxine plasma levels. ?Avoid strong CYP2D6 inhibitors*.
 - ❖ Potential adverse effects include marked increase in BP, severe anticholinergic side effects and serotonin syndrome ^(27,28).
-
- ❖ Up to 150mg bd venlafaxine was added to high dose clomipramine / imipramine. No significant changes in BP, heart rate, ECG or tricyclic levels were found.
-
- ❖ Doses of nefazodone used are typically 100-200mg bd.
 - ❖ SSRI inhibition of nefazodone metabolism via CYP2D6 may lead to possible accumulation of active metabolite, which can cause anxiety & irritability. Avoid strong inhibitors of CYP2D6*. Case reports of SS with paroxetine & fluoxetine ^(30,31).
 - ❖ May help with SSRI-induced sexual dysfunction.

*Fluoxetine and paroxetine are the most potent CYP2D6 inhibitors

Conclusion

A recently published review ⁽¹⁾ on this topic concluded that there is limited evidence, mostly in uncontrolled studies, supporting the efficacy of combination antidepressant treatment. As shown in the table, there are very few randomised, controlled trials and sample sizes are small. Most studies use open-label treatment and therefore placebo effects cannot be ruled out. Different definitions of treatment resistance, outcome measures and treatment response were used in the studies.

Due to these limitations, combining antidepressants **cannot** be recommended as first-line therapy for refractory depression. However, some patients who have been unresponsive to monotherapy may improve with combination treatment, though more established methods such as ECT or lithium/thyroid augmentation should be tried first. Further randomised controlled trials with larger sample sizes are required to demonstrate the efficacy and safety of combination strategies for treatment resistant depression.

References

1. Lam RW, Wan DDC, Cohen NL, Kennedy SH. Combining antidepressants for treatment-resistant depression: a review. *J Clin Psychiatry* 2002;63:685-693.
 2. Fava M. Augmentation and combination strategies in treatment-resistant depression. *J Clin Psych* 2001;62(suppl. 18):4-11.
 3. Amsterdam JD, Garcia-Espana F, Rosenzweig M. Clomipramine augmentation in treatment-resistant depression. *Depress Anxiety* 1997;5:84-90.
 4. Berlanga C, Ortega-Soto HA. A 3-year follow-up of a group of treatment-resistant depressed patients with a MAOI/tricyclic combination. *J Affect Disord* 1995;34:187-192.
 5. Sethna ER. A study of refractory cases of depressive illnesses and their response to combined antidepressant treatment. *Br J Psychiatry* 1974;124:265-272.
 6. Davidson J, McLeod M, Law-Yone B et al. A comparison of electroconvulsive therapy and combined phenelzine-amitriptyline in refractory depression. *Arch Gen Psychiatry* 1978;35:639-642.
 7. Schmauss M, Kapfhammer HP, Meyr P, et al. Combined MAO-inhibitor and tri-(tetra) cyclic antidepressant treatment in therapy resistant depression. *Prog Neuropsychopharmacol Biol Psychiatry* 1988;12:523-532.
 8. Bazire S. Depression. In: *Psychotropic Drug Directory*, United Kingdom: Mark Allen, 2001:54.
 9. DeBattista C, Sofuoglu M, Schatzberg AF. Serotonergic synergism: the risks and benefits of combining the selective serotonin reuptake inhibitors with other serotonergic drugs. *Biol Psych* 1998;44(5):341-7.
 10. Joffe RT, Bakish D. Combined SSRI-moclobemide treatment of psychiatric illness. *J Clin Psychiatry* 1994;55:24-25.
 11. Hawley CJ, Quick SJ, Ratnam S et al. Safety and tolerability of combined treatment with moclobemide and SSRIs: a systematic study of 50 patients. *Int Clin Psychopharmacol* 1996;11:187-191.
 12. Levitt AJ, Joffe RT, Kamil R et al. Do depressed subjects who have failed both fluoxetine and a tricyclic antidepressant respond to the combination? *J Clin Psychiatry* 1999;60:613-616.
 13. Weilburg JB, Rosenbaum JF, Biederman J et al. Tricyclic augmentation of fluoxetine. *Ann Clin Psychiatry* 1991;3:209-213.
 14. Zajecka JM, Jeffries H, Fawcett J. The efficacy of fluoxetine combined with a heterocyclic antidepressant in treatment-resistant depression: a retrospective analysis. *J Clin Psychiatry* 1995;56:338-343.
 15. Fava M, Rosenbaum JF, McGrath PJ et al. Lithium and tricyclic augmentation of fluoxetine treatment for resistant major depression: a double-blind, controlled study. *Am J Psychiatry* 1994;151:1372-1374.
 16. Seth R, Jennings AL, Bindman J et al. Combination treatment with noradrenaline and serotonin reuptake inhibitors in resistant depression. *Br J Psychiatry* 1992;161:562-565.
 17. Weilburg JB, Rosenbaum JF, Biederman J et al. Fluoxetine added to non-MAOI antidepressants converts nonresponders to responders: a preliminary report. *J Clin Psychiatry* 1989;50:447-449.
 18. Nierenberg AA, Cole JO, Glass L. Possible trazodone potentiation of fluoxetine: a case series. *J Clin Psychiatry* 1992;53:83-85.
 19. Bondolfi G, Chautems C, Rochat B et al. Non-response to citalopram in depressive patients: pharmacokinetic and clinical consequences of a fluvoxamine augmentation. *Psychopharmacology* 1996;128:421-425.
 20. Hunchak J. SSRI combination treatment for depression (letter). *Can J Psychiatry* 1997;42:531-532.
 21. Carpenter LL, Jovic Z, Hall JM et al. Mirtazapine augmentation in the treatment of refractory depression. *J Clin Psychiatry* 1999;60:45-49.
 22. Carpenter LL, Yasmin S, Price LH. A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. *Biol Psychiatry* 2002;51:183-188.
 23. Debonnel G, Gobbi G, Turcotte N, Boucher N, Hebert C et al. Effects of mirtazapine, paroxetine and their combination: a double-blind study in major depression. *J Eur Coll Neuropsychopharm* 2000;10(suppl.3):S252.
 24. Lucca A, Serretti A, Smeraldi E. Effect of reboxetine augmentation in SSRI resistant patients. *Hum Psychopharmacol Clin Exp* 2000;15:143-145.
 25. Devarajan S, Dursun SM. Citalopram plus reboxetine in treatment-resistant depression (letter). *Can J Psychiatry* 2000;45:489-490.
 26. Fleishaker JC, Herman BD, Pearson LK, Ionita A, Mucci M. Evaluation of the potential pharmacokinetic /pharmacodynamic interaction between fluoxetine and reboxetine in healthy volunteers. *Clin Drug Invest* 1999;18:141-150.
 27. Bhatara VS, Magnus RD, Paul KL et al. Serotonin syndrome induced by venlafaxine and fluoxetine: a case study in polypharmacy and potential pharmacodynamic and pharmacokinetic mechanisms. *Ann Pharmacother* 1998;32:432-436.
 28. Benazzi F. Venlafaxine-fluoxetine interaction. *J Clin Psychopharmacol* 1999;19:96-98.
 29. Gomez JM, Perramon CT. Combined treatment with venlafaxine and tricyclic antidepressants in depressed patients who had partial response to clomipramine or imipramine: initial findings. *J Clin Psychiatry* 2000;61:285-289.
 30. Smith DL, Wenegrat BG. A case report of serotonin syndrome associated with combined nefazodone and fluoxetine (letter). *J Clin Psychiatry* 2000;61:146.
 31. John L, Perreault MM, Tao T et al. Serotonin syndrome associated with nefazodone and paroxetine. *Ann Emerg Med* 1997;29:287-289.
- Stahl S. *Newer Antidepressants and Mood Stabilisers*. In: *Essential Psychopharmacology*, 2nd ed. United Kingdom: Cambridge University Press, 2001:271-295.

Acknowledgement

This article was prepared by Kate Smith and reviewed by members of the Pharmacy Department.
Comments are welcome at the e-mail address: Druginformation.Graylands@health.wa.gov.au