Treatment of Depression and Anxiety - current information

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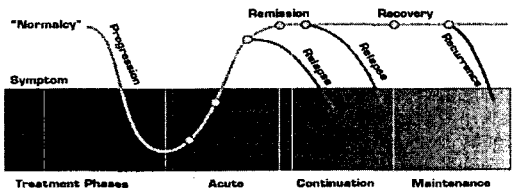
Conclusions - 5 main points

1. Remission very important to aim for clinically - best achieved early on
2. Mechanism of action for dual action drug superiority probably due to 5-HT and NE interactions - higher doses required to get dual action effects
3. Dual Action drugs produce more remission than SSRIs - clinically relevant - most evidence for Venlafaxine XR - IR may not be as effective
4. Comorbidity of depression and anxiety is the rule not the exception
5. Depression and anxiety VERY common in medically ill patients and needs to be diagnosed much more frequently - always ask screening question

Section 1. Remission

Course and Outcome of Depression



Response

- Response is a reduction in the signs and symptoms of depression
  - >50% decrease from baseline for the HAM-D or MADRS
- Response is the endpoint for clinical trials, not clinical practice
- Many responders have residual symptoms and are therefore have only partial remission

Remission

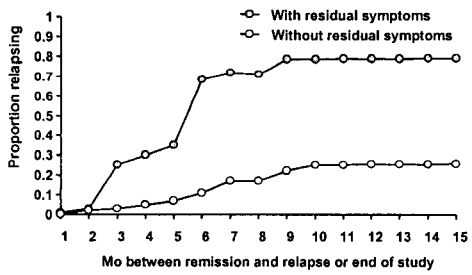
- Remission is defined as a HAM-D score less than 8 or a CGI of 1.
- A patient who is in remission may be considered asymptomatic or well.
- Remission is a more relevant endpoint for clinicians, as it signifies that the patient is "well."

The Residual Depressive Syndrome

- Neglected in research
- 17-item HAM-D score of ≥8
- Common: 32% after 15 months (n=60)
- Symptoms:
  - — Mood (depressed, anxious)
  - — Negative thought content (guilt, hopelessness)
  - — Impairment of work and activities
  - — Anorexia, early insomnia
- Predicts relapse/recurrence: 76% (13/17)

Paykel ES, et al. *Psychopathology* 1998;31:5-14.

Proportion of Patients With and Without Residual Symptoms Relapsing After Remission



Paykel et al. Psychol Med 1995;25:1171

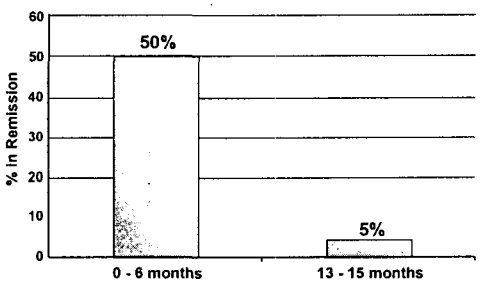
Implications of incomplete treatment of Depression

- Increased relapse rates
  - Faravelli et al., (1986)
  - Simons et al., (1986)
  - Evans et al., (1992)
- Continuing functional impairment
  - Mintz et al., (1992)
- Continuing increase in suicide rate

Importance of Reaching Remission very important clinically

Also, Importance of Reaching Remission Early very important

Achieving Remission: When Are The Chances Greatest?



Keller M. 1992

Aim of Treatment

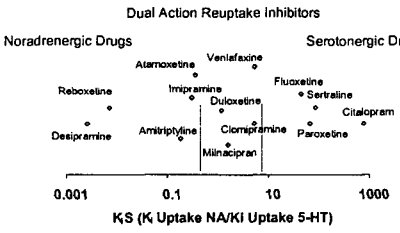
- Response is NOT sufficient: Remission is the goal of treatment
- If residual symptoms are present there is a need for vigorous and aggressive treatment
- *Achieving remission most likely early in treatment*, so best treatment should be given at start and not reserved.

Section 2. Are two mechanisms of action better?

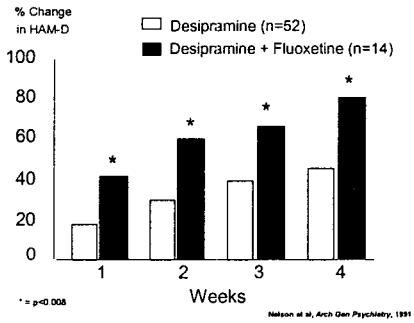
What clinical evidence is there to suggest that dual-action drugs (such as venlafaxine) are better than single action drugs (such as SSRIs)?

Are Two better than one?

Selectivity of Antidepressants for serotonin and noradrenaline reuptake

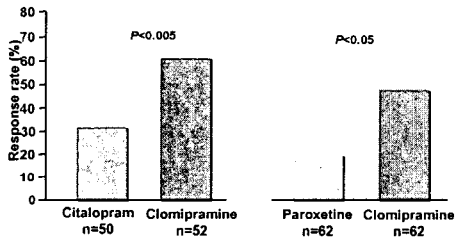


Combining Antidepressants



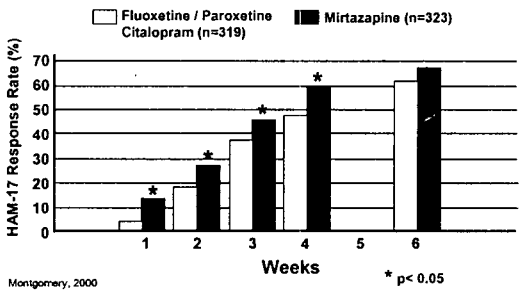
Nelson et al, *Arch Gen Psychiatry*, 1991

Remission or "Complete Response" (HAM-D) in Inpatients With Major Depression



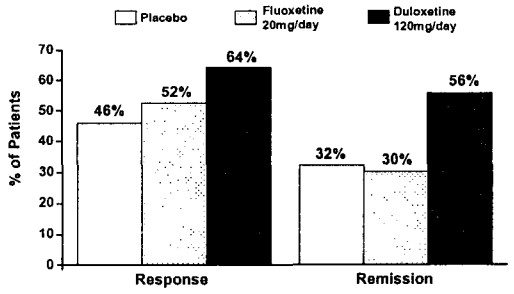
DUAG. J Affect Disord 1990;18:289
DUAG. Psychopharmacology 1986;90:131; Ferrier IN. J Clin Psychiatry 1999;60:10

Mirtazapine Has A Higher Response Rate Than SSRIs In The First 4 Weeks - #1



Montgomery, 2000

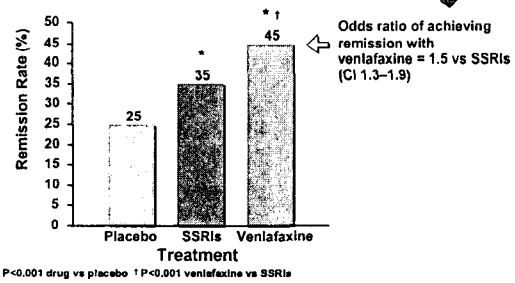
Duloxetine Has Higher Remission Rates Than Fluoxetine - #2



Goldstein DJ, et al. J Clin Psychiatry. 2002;63(3):225-231.

Remission Pooled Analysis

Remission Rates



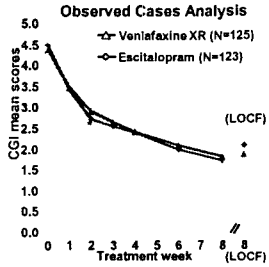
* P<0.001 drug vs placebo † P<0.001 venlafaxine vs SSRIs

Thase ME, et al. Br J Psychiatry. 2001;178:234-241

Copying doesn't work

Some drugs try and copy the effectiveness of dual-action drugs with poor studies - but it doesn't work

Assessing comparable dosing in RCTs



Dose Assessment

	Ven XR	Esc
Mean doses at week 8	95.2 mg/d	12.1 mg/d
Dose range in study	75-150 mg/d	10-20 mg/d
Therapeutic dose range	75-225 mg/d	10-20 mg/d
% max dose	42%	61%

Montgomery et al. *Eur Neuropsychopharmacol* 2002; 12 (Suppl 3): S254, Abstract P.1.206.
Montgomery et al. Presented at ECNP, Barcelona, Spain, 2002.

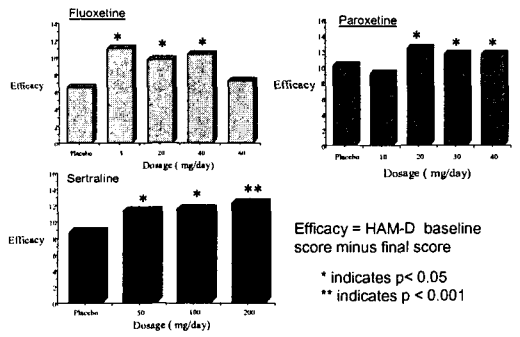
*p<0.05 vs venlafaxine XR.

Are Two better than one?

YES!

Section 3. Dose Response

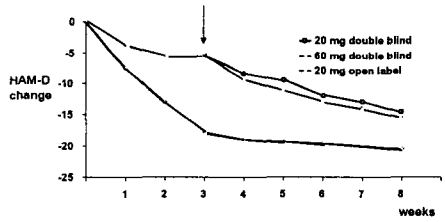
Dose Response of SSRIs



Efficacy = HAM-D baseline score minus final score

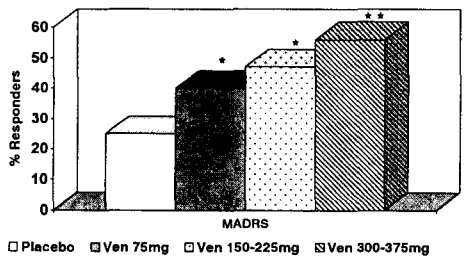
* indicates p< 0.05
** indicates p < 0.001

Lack of Effect of Increasing Dose of Fluoxetine



(Dornseif BE et al ,1989)

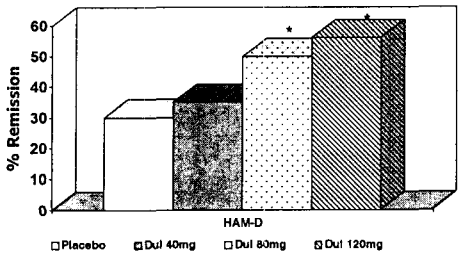
Venlafaxine Dose Response - Rates in Outpatients



*p<0.05

Adapted from Schweizer et al. (1991) J Clin Psychopharmacology 11:233-6

Duloxetine Dose Response - Rates in Outpatients



Goldstein DJ, et al. J Clin Psychiatry. 2002;63(3):225-231
Data on file, Lilly Research Laboratories. Study F1J-MC-HMATb.

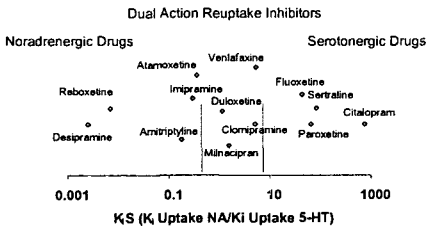
Hypothesis:

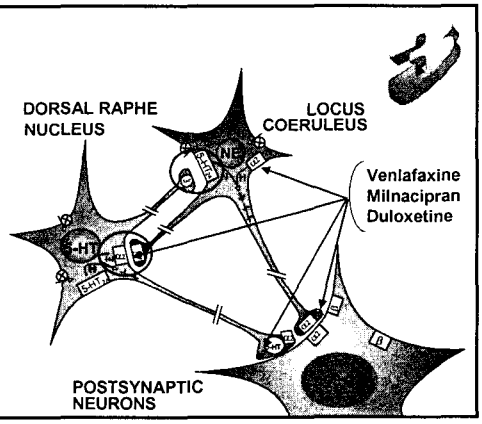
Two is better than one

Dose increases make a difference for dual-action drugs, but not for SSRIs

Why?

Selectivity of Antidepressants for serotonin and noradrenaline reuptake





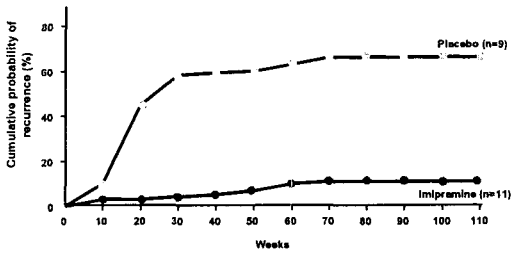
Maintenance therapy: unresolved issues

- Duration of maintenance antidepressant medication (ADs)?
- Does long-term use of ADs increase rate of relapse/recurrence after cessation of use?
- Do ADs lose efficacy/potency over time?
- Correct maintenance dose?
- Correct rate of tapering ?
- Role of maintenance psychotherapy?

Long-term issues

Long-term outcome of major depression

Subjects who were recovered on imipramine for 3 years and then randomized to imipramine or placebo. Mean dose of imipramine at year 5, 236 mg/day

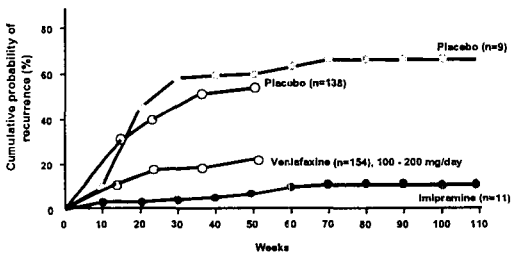


p=0.006 by Mantel-Cox test

Adapted from Kupfer et al. *Arch Gen Psychiatry* 1992; 49: 769-773.

Long-term outcome of major depression

Patients in remission following 6 months venafaxine therapy (mean final dose 151 mg/day) entered into 12 month study that compared continued venlafaxine therapy with placebo on recurrence of depression. Recurrence of depression was defined as CGI-S score ≥4

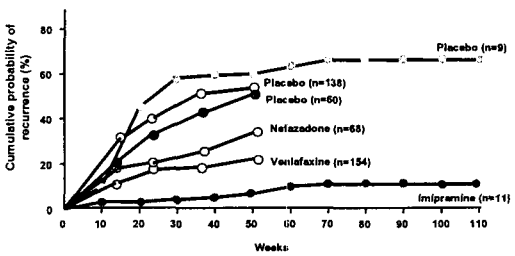


p<0.001 venlafaxine XR vs placebo

Adapted from Kunz et al. Presented at AEP 2000, Prague.

Long-term outcome of major depression

Patients in remission following 3 months nefazadone treatment, with or without cognitive psychotherapy (Keller et al, 2000), entered into a 12 month follow-up study that compared continued nefazadone therapy with placebo on recurrence of depression.



p<0.04 nefazadone XR vs placebo

Adapted from Keller et al in preparation 2002.

Maintenance therapy: unresolved issues

- Duration of maintenance antidepressant medication (ADs)?
- Does long-term use of ADs increase rate of relapse/recurrence after cessation of use?
- Do ADs lose efficacy/potency over time?
- Correct maintenance dose?
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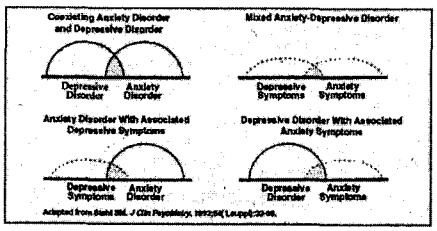
Section 4 - Comorbidity - psychiatric

Relationship Between Depressive Symptoms and Anxiety Symptoms



Major Depressives With Significant Anxiety

- *More severe symptoms*
- Increased psychosocial impairment
- More likely to be disabled[1]
  - 48% of those with comorbid MDD and Anxiety Disorder
  - 39% of those with either illness alone
- Chronic course
- Poorer outcome
- Greater vulnerability to suicide

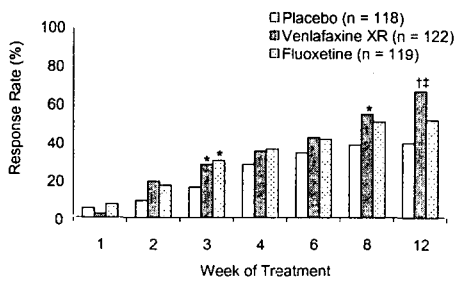
[1] *Sartorius, Br J Psychiatry, 1986, 168 (Suppl 30), 38-43*

Venlafaxine XR and Fluoxetine in Depressed Outpatients With Concomitant Anxiety

- 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel study
- Outpatients with DSM-IV major depression and
  - baseline HAM-D ≥ 20
  - Covi score > 8
  - symptoms of depression for at least 1 month
  - Venlafaxine XR 75 to 225 mg/day or fluoxetine 20 to 60 mg/day

Silverstone et al, J Clin Psych, 1999

HAM-A Response Rate



* $p \leq 0.05$, † $p \leq 0.001$ vs. placebo
‡ $p \leq 0.05$ vs. fluoxetine

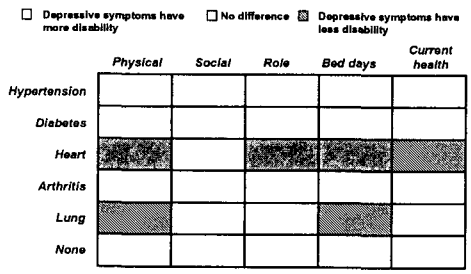
Recent comorbidity studies

- 60% of MDD patients have comorbid Axis I disorders (epidemiology study of 7,760 patients)[1]
- 64% of MDD patients have comorbid Axis I disorders (study in 478 MDD patients), with 57% having a comorbid anxiety disorder[2]
- 79% of MDD patients have comorbid Axis I and II disorders (study in 269 patients), with 57% having an anxiety disorder[3]
- "Comorbidity of depression with other psychiatric disorders is the rule, not the exception"[4]

[1] de Graff et al, Am J Psychiatry, 2002
[2] Zimmerman et al, J Clin Psychiat, 2002
[3] Melartin et al, J Clin Psychiat, 2002
[4] Rapaport, J Clin Psychiat, 2001

Section 4 - Comorbidity - medical

Depressive symptoms vs chronic medical conditions on daily functioning disability



Wells et al. JAMA 1989; 262: 914-919.

Depression in the medically ill-1

- Depression common in medically ill patients
- More common with certain chronic illnesses
  - Chronic Pain
  - Gastrointestinal disorders (Ulcers)
  - Neurological disorders (Epilepsy, Stroke, Migraine, Multiple sclerosis)

Depression in the medically ill-2

- Up to 25% will have depression as a significant symptom
- However, up to 80% of these will not be recognized, particularly in in-patients
- Partly due to difficulty in distinguishing depression from "appropriate sadness"
- However, internal medicine, cardiology, gastrotenterology, and obsetric and gynaecology specialists have shown no improvement in recognition rates in last 25 years

Depression in the medically ill-3

- Physical symptoms a common presentation
- Common symptoms include the following
  - Vague pain
  - Backache
  - Insomnia
  - Fatigue
- Also varies between cultures

Concise assessment scale for Depression - screening question

- Over the past week have you been feeling sad, upset, or low in mood?
- If so, has this been present on average more than 50% of each day?

If no to either question, stop there. If yes, then continue

Remember to ask ALL patients

Treatment for anxiety and depression in the UK ICD-10 interview survey (n=10,108)

Any treatment, pharmacological or psychotherapy

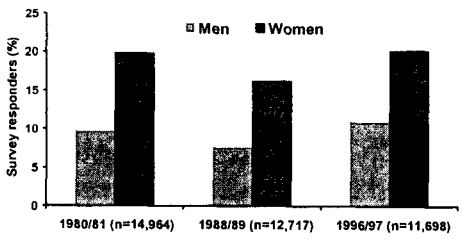
- 8% of GAD cases (n=302)
- 14% of panic disorder cases (n=81)
- 19% of OCD cases (n=118)
- 11% of anxiety / depressive cases (n=752)
- 28% of depression cases (n=206)

OVER 70% OF CASES OF DEPRESSION AND ANXIETEY NEVER DIAGNOSED OR TREATED

N.B. The likelihood of treatment increased with symptom severity

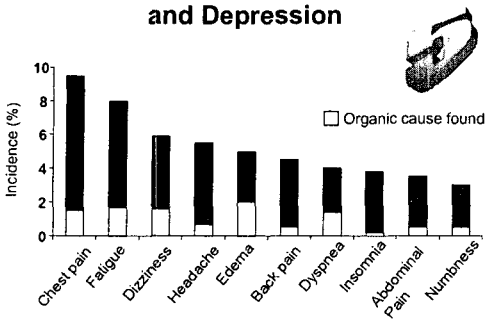
Bebbington et al. *Psychol Med* 2000; 30: 1359-1376

Do you currently suffer from worry, anguish, or anxiety?



Statistics Sweden

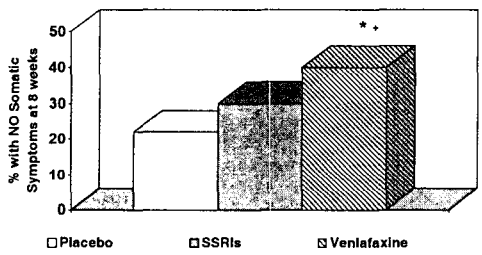
Presenting Symptoms for Anxiety (GAD) and Depression



Kroenke K, Mangelsdorff AD. Am J Med 1989;86:262

Venlafaxine - Effective in Somatic Symptoms

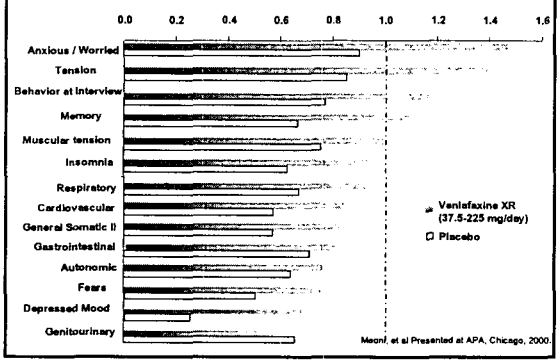
Pooled analysis - 2,046 depressed patients



*p<0.05 vs placebo
+p<0.05 vs SSRIs

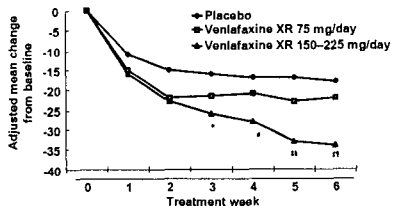
Thase ME, et al. Br J Psychiatry. 2001;178:234-241

The HAM-A Scale: effect size at 6 months in GAD



Meoni, et al Presented at APA, Chicago, 2000.

Effexor XR = "Pain Relief" in Diabetic Neuropathy



Conclusions - 5 main points

1. Remission very important to aim for clinically - best achieved early on
2. Dual Action drugs produce more remission than SSRIs - clinically relevant
3. Mechanism of action for dual action drug superiority probably due to 5-HT and NE interactions - higher doses required to get dual action effects
4. Comorbidity is the rule not the exception, and evidence for superiority of venlafaxine in both comorbid anxiety and depression
5. Depression and anxiety VERY common in medically ill patients and needs to be diagnosed much more frequently - always ask screening question