Northern Centre for Mood Disorders

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Institute of Neuroscience

Multi-Therapy Resistant Depression: Clinical utility of the concept and treatment options to consider

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Disclosure / conflict of interest

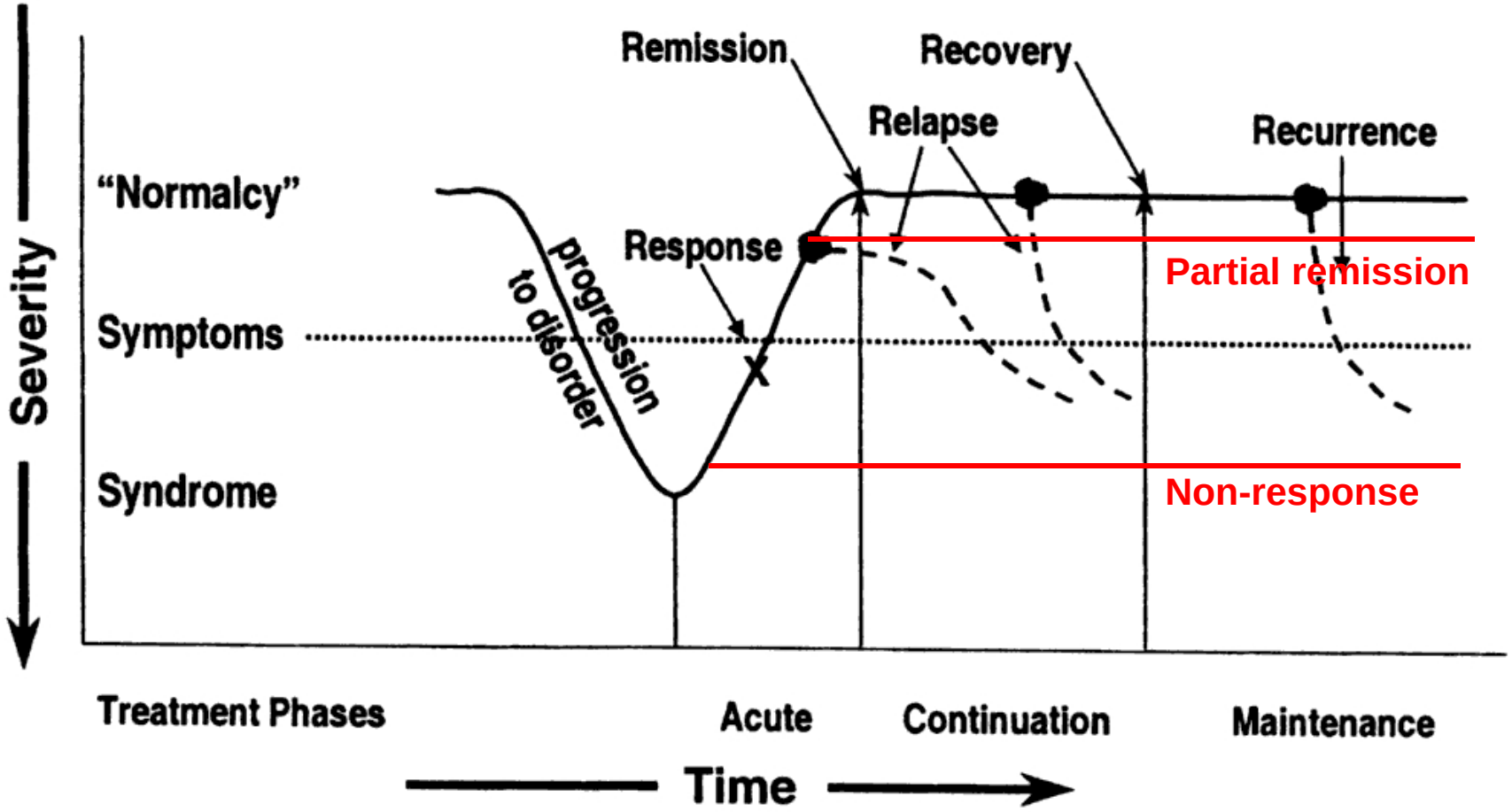
I work clinically in a tertiary level specialist affective disorders service in Northumberland Tyne and Wear NHS FT

I have an interest in relation to one or more organisations that could be perceived as a possible conflict of interest in the context of the subject of this presentation. The relationships are summarised below:

Interest	Name of organisation
Speaker fees	AstraZeneca, Bristol Myers-Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Merck Sharp & Dohme, Pfizer, Servier, Wyeth
Consultancy fees	AstraZeneca, Bristol Myers-Squibb, Cyberonics, Eli Lilly, Janssen-Cilag, LivaNova, Lundbeck, Merck Sharp & Dohme, Servier, Wyeth
Independent investigator-led research support	AstraZeneca, Eli Lilly, Wyeth

I do not hold any shares in, nor have any ongoing financial relationship with, any pharmaceutical company

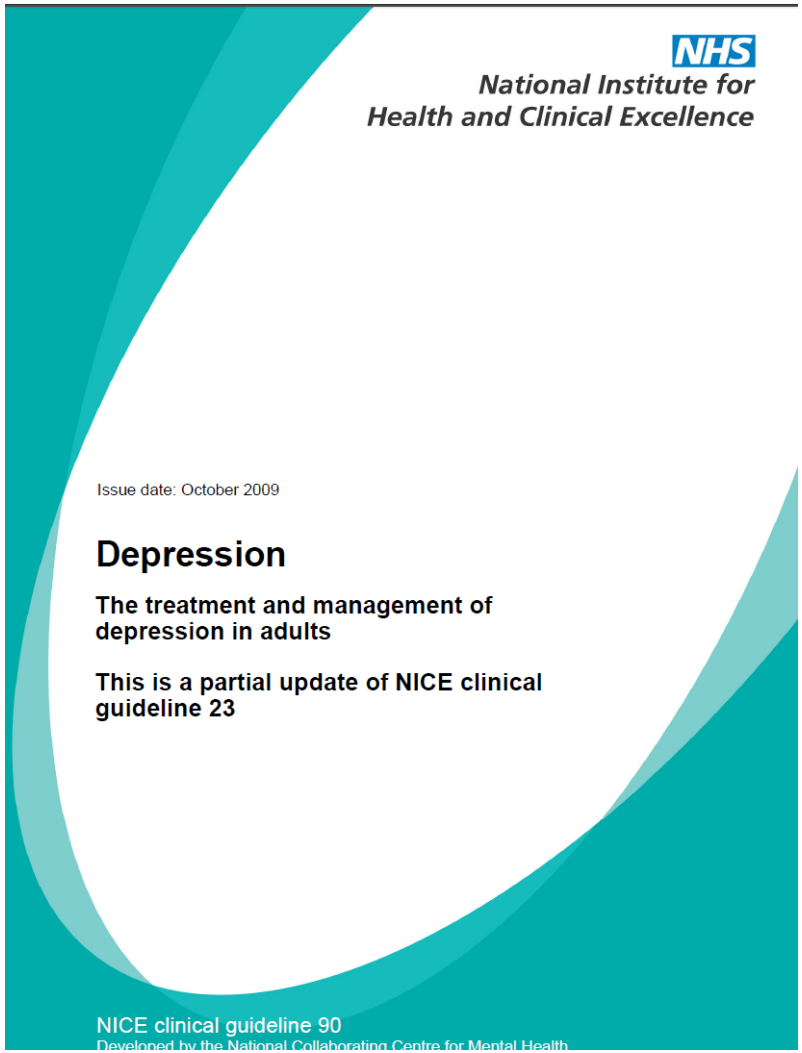
Model of depression and treatment



Frank et al 1991

Guidelines – NICE & BAP

2009



2015

BAP Guidelines

Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines

Psychopharm

Journal of Psychopharmacology
2015, Vol. 29(5) 459–525

DOI: 10.1177/0269881115581093
jop.sagepub.com
SAGE

Anthony Cleare[1], CM Pariante[2] and AH Young[3]
With expert co-authors (in alphabetical order):
IM Anderson[4], D Christmas[5], PJ Cowen[6], C Dickens[7], IN Ferrier[8], J Geddes[9], S Gilbody[10], PM Haddad[11], C Katona[12], G Lewis[12], A Malizia[13], RH McAllister-Williams[14], P Ramchandani[15], J Scott[16], D Taylor[17], R Uher[18] and the members of the Consensus Meeting[19]
Endorsed by the British Association for Psychopharmacology

Abstract
A revision of the 2008 British Association for Psychopharmacology evidence-based guidelines for treating depressive disorders with antidepressants was undertaken in order to incorporate new evidence and to update the recommendations where appropriate. A consensus meeting involving experts in depressive disorders and their management was held in September 2012. Key areas in treating depression were reviewed and the strength of evidence and clinical implications were considered. The guidelines were then revised after extensive feedback from participants and interested parties. A literature review is provided which identifies the quality of evidence upon which the recommendations are made. These guidelines cover the nature and detection of depressive disorders, acute treatment with antidepressant drugs, choice of drug versus alternative treatment, practical issues in prescribing and management, next-step treatment, relapse prevention, treatment of relapse and stopping treatment. Significant changes since the last guidelines were published in 2008 include the availability of new antidepressant treatment options, improved evidence supporting certain augmentation strategies (drug and non-drug), management of potential long-term side effects, updated guidance for prescribing in elderly and adolescent populations and updated guidance for optimal prescribing. Suggestions for future research priorities are also made.

Keywords
Antidepressants, depression, depressive disorder, treatment, evidence-based guidelines

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[18]Associate Professor, Canada Research Chair in Early Interventions, Dalhousie University, Department of Psychiatry, Halifax, NS, Canada
[19]Other members of the consensus meeting: Prof David Baldwin, Prof Thomas Barnes, Dr David Coghill, Prof Guy Goodwin, Prof Tony Hale, Prof Louise Howard, Prof Brian Leonard, Dr Alan Lenox-Smith, Prof Keith Matthews, Dr Stuart Montgomery, Prof Ian Reid, Prof Barbara J Sahakian, Dr Orla White.

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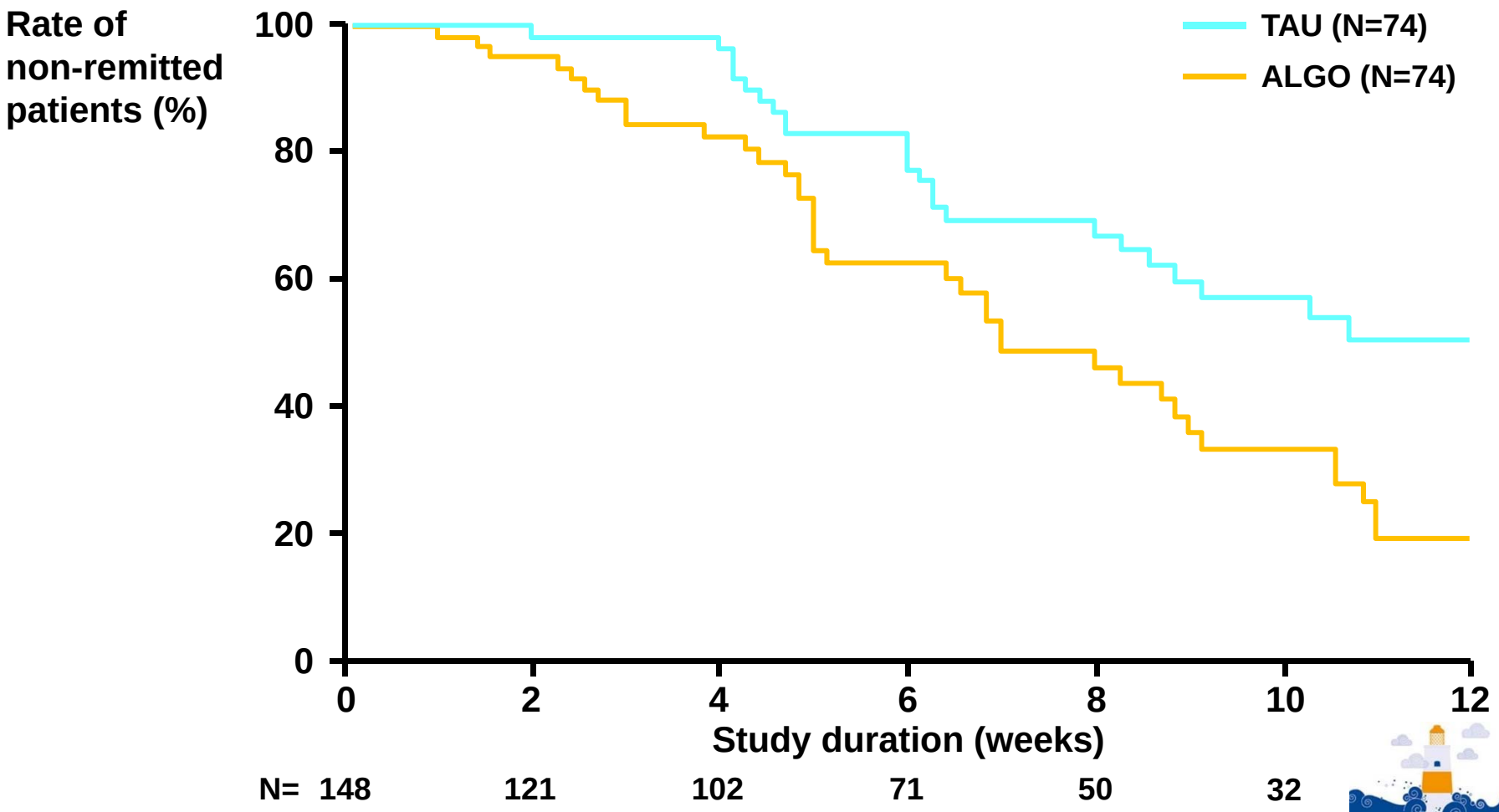
Maximising outcomes in depression

- Avoid delays
- Clear pharmacological strategy
- Use adequate trials of medication
- Holistic treatment
- Monitor response and use critical decision points
- Avoid therapeutic nihilism and instil hope

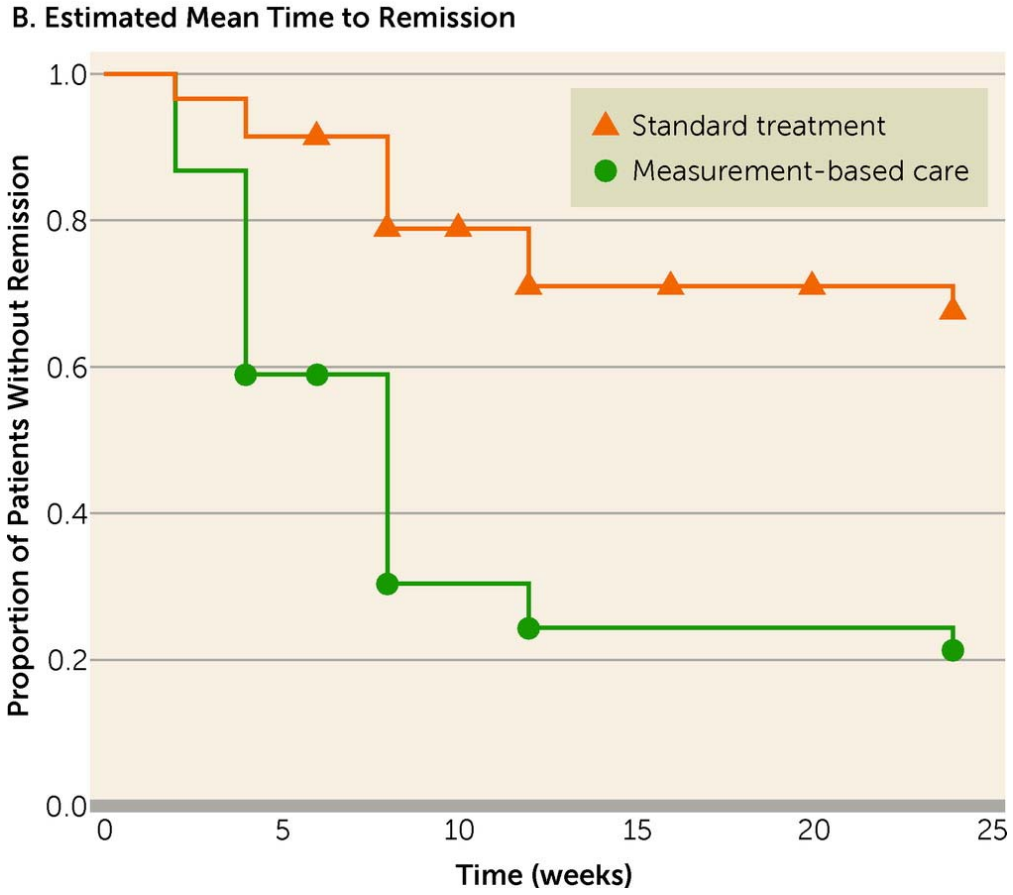
Treatment by algorithm (ALGO) vs treatment as usual (TAU)



HR=2.0 (p=0.004)
Survival analysis (ITT group)

Bauer et al. *J Clin Psychopharmac*

"Measurement Based Care (MBC)"
(guideline- and rating scale-based decisions)



- Outpatients with moderate to severe MDD
- Randomized to 24 weeks of either MBC (N=61) or standard treatment (N=59).
- Pharmacotherapy restricted to paroxetine (20–60 mg/day) or mirtazapine (15–45 mg/day)

The MBC group had significantly more treatment adjustments (44 compared with 23) and higher antidepressant dosages from week 2 to week 24.

Guo, T. et al. (2015) Measurement-Based Care Versus Standard Care for Major Depression: A Randomized Controlled Trial With Blind Raters. Am J Psych 172(10): 1004-1013.

BAP Guidelines – choice of antidepressant

- In the absence of special factors:
  - choose antidepressants that are better tolerated and safer in overdose (S).
    - most evidence for SSRIs
      - with other newer antidepressants these are first line choices
    - Older TCAs reserved for if first line drug treatment has failed (D)
    - MAOIs not first line and should only be initiated by practitioners with expertise in treating mood disorders (D).
      - ***BUT NB*** *factors influencing choice of antidepressant:*

        presence of atypical features (responds less well to imipramine than phenelzine)
- In more severely ill patients, and where maximising efficacy is of overriding importance, consider:
  - Amitriptyline, clomipramine, venlafaxine (≥ 150 mg), escitalopram (20 mg), sertraline, mirtazepine

BAP Guidelines – Augmentation options

- Augmentation options 'sequenced':
  - First line: consider adding quetiapine (A), aripiprazole (A) or lithium (A)
  - Second line risperidone (A), olanzapine (B), tri-iodothyronine (B) or mirtazapine (B)
  - Other additions that could be considered bupropion (B), buspirone (B), lamotrigine (C) and tryptophan (C)
  - Recommended for use in specialist centres with careful monitoring (S) modafinil (C), stimulants (C), oestrogen in perimenopausal women (C) and testosterone in men with low testosterone levels (C).

Preserving hope

- What do you do if you have exhausted all options included in the guidelines for routine use?
- Is it sensible to keep trying endless trials of monoaminergic treatments?
- What other treatment options are available?
- When should such treatments (and/or referral to specialist services) be considered?

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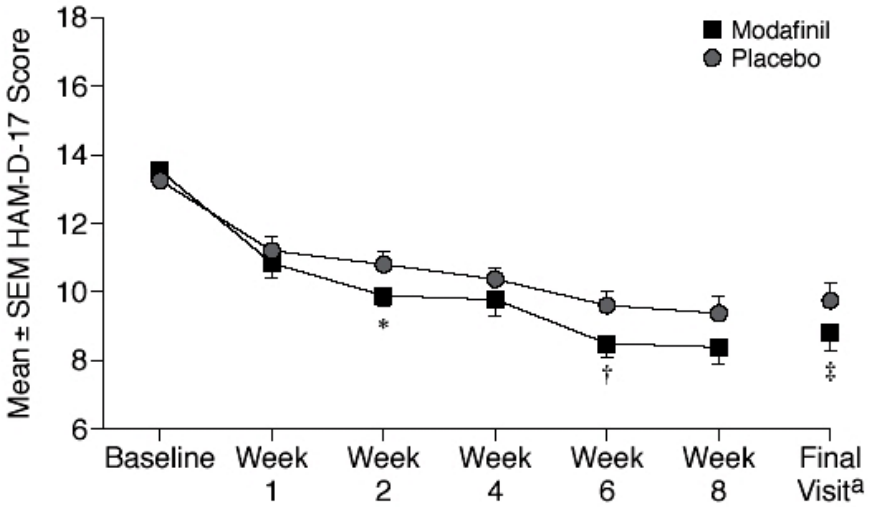
Modafinil augmentation of SSRIs

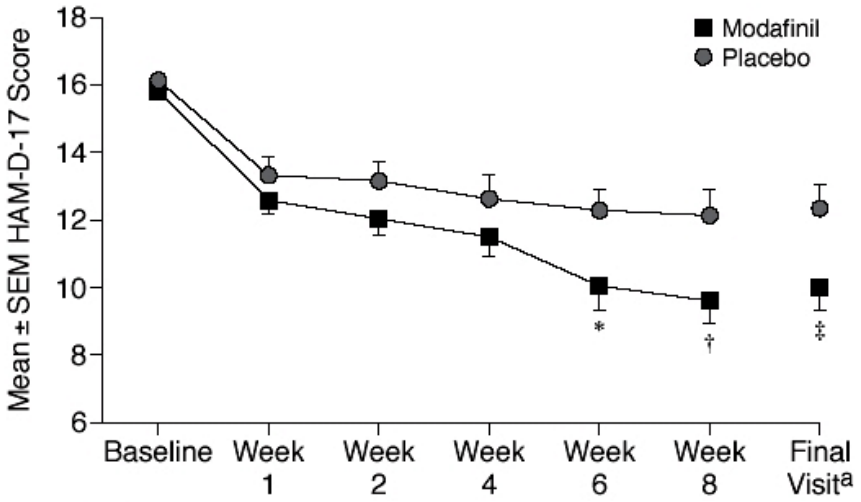
Patients with excessive fatigue or sleepiness despite adequate SSRI ≥ 8weeks

All



[a]Modafinil, N = 151; placebo, N = 149 at endpoint.
*p = .07; mean difference in change = 1.1.
†p = .06; mean difference in change = 1.1.
‡p < .08; mean difference in change = 1.2.

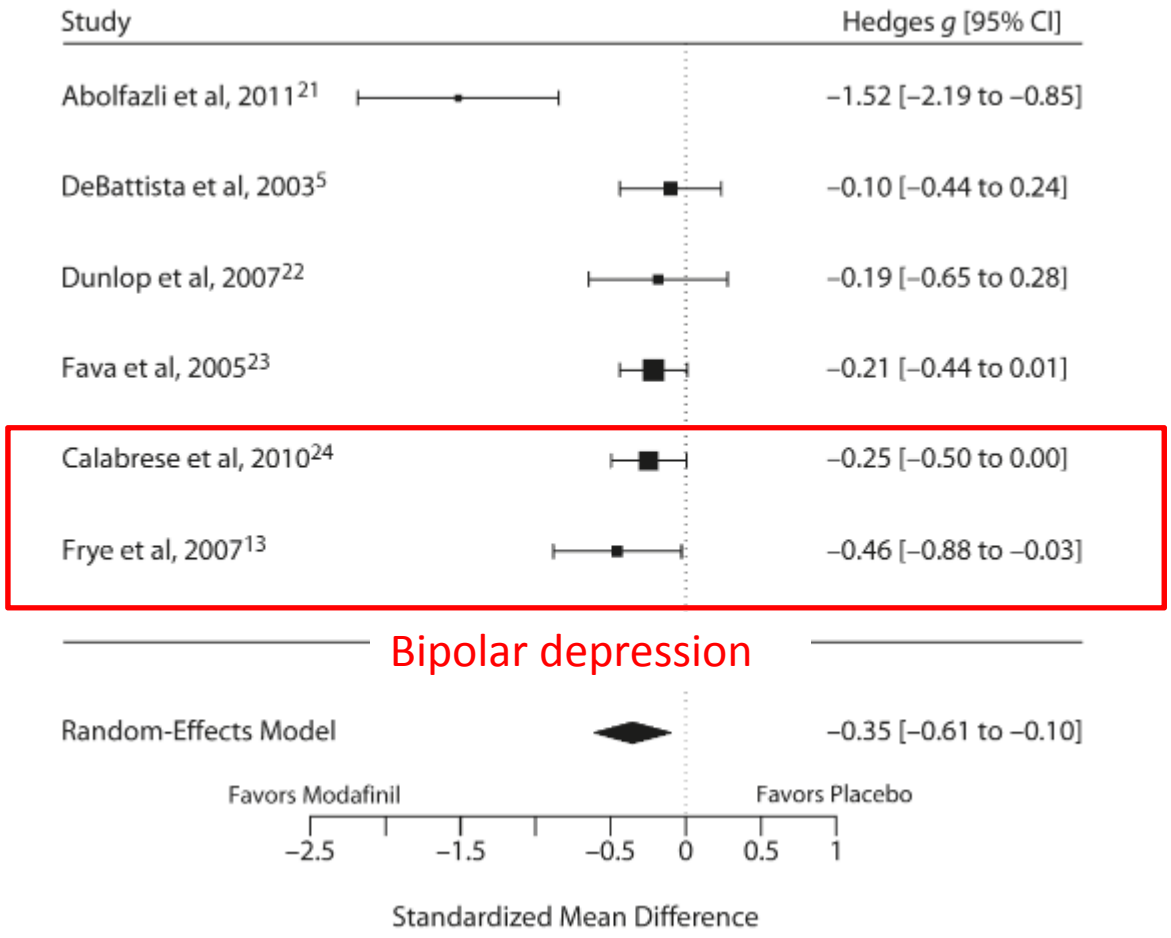
$HAMD_{17}$ ≥14



[a]Modafinil, N = 85; placebo, N = 65 at endpoint.
*p = .04; mean difference in change = 1.9.
†p = .04; mean difference in change = 2.4.
‡p = .05; mean difference in change = 2.2.

Fava et al 2005

Modafinil augmentation: meta-analysis



Goss et al. 2013 J Clin Psychiatry 74:1101-1107

Other psychostimulants?

- Systematic review – Abbasowa et al. 2013 Nordic J Psych
  - Examined modafinil, methylphenidate, dexamphetamine, methylamphetamine and pemoline
    - 2 RCTs for modafinil – positive
    - No clear evidence for efficacy of other stimulants

- Lavretsky et al. 2015 Am J Psych
  - RCT of citalopram vs methylphenidate vs combo in elderly depressed patients (n=47-48 in each group)
  - Largest response in combo group. Well tolerated.

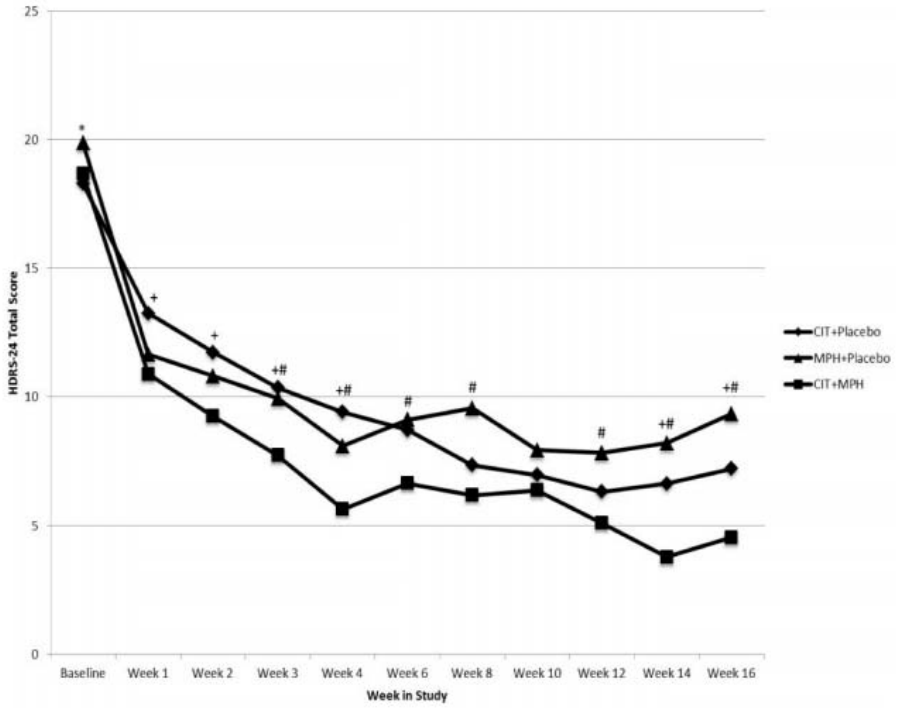


Figure 2.
Change in HDRS-24 scores by treatment condition over the 16-week period
Citalopram=CIT; Methylphenidate=MPH; Placebo=PBO
*Statistically significant difference between CIT+PBO and MPH+PBO, p<.05
+ Statistically significant difference between CIT+PBO and CIT+MPH, p<.05
# Statistically significant difference between MPH+PBO and CIT+MPH, p<.05

Transdermal selegiline

- Pooled analysis of 5 PC-RCTs of STS
  - 352 atypical; 932 non-atypical patients
  - Overall significant benefit of STS
  - Effect numerically larger in atypical patients

  Pae et al. 2013 CNS Spectrums 19, 324–329
- STS approved by US FDA in 2006

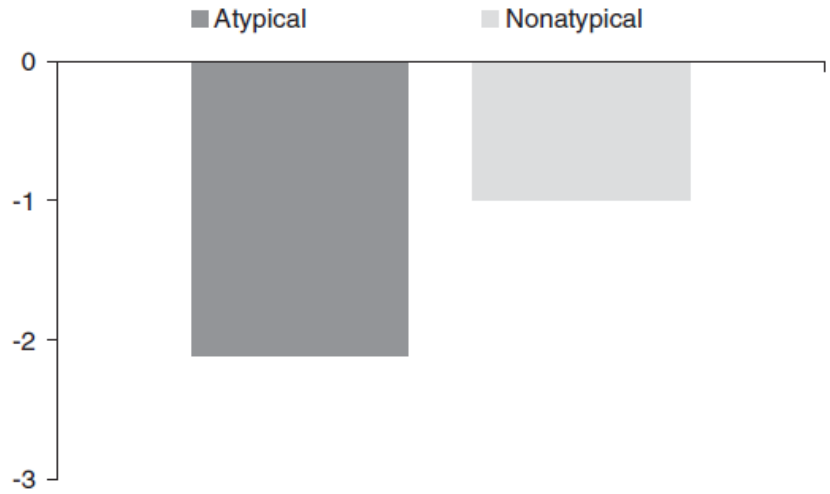
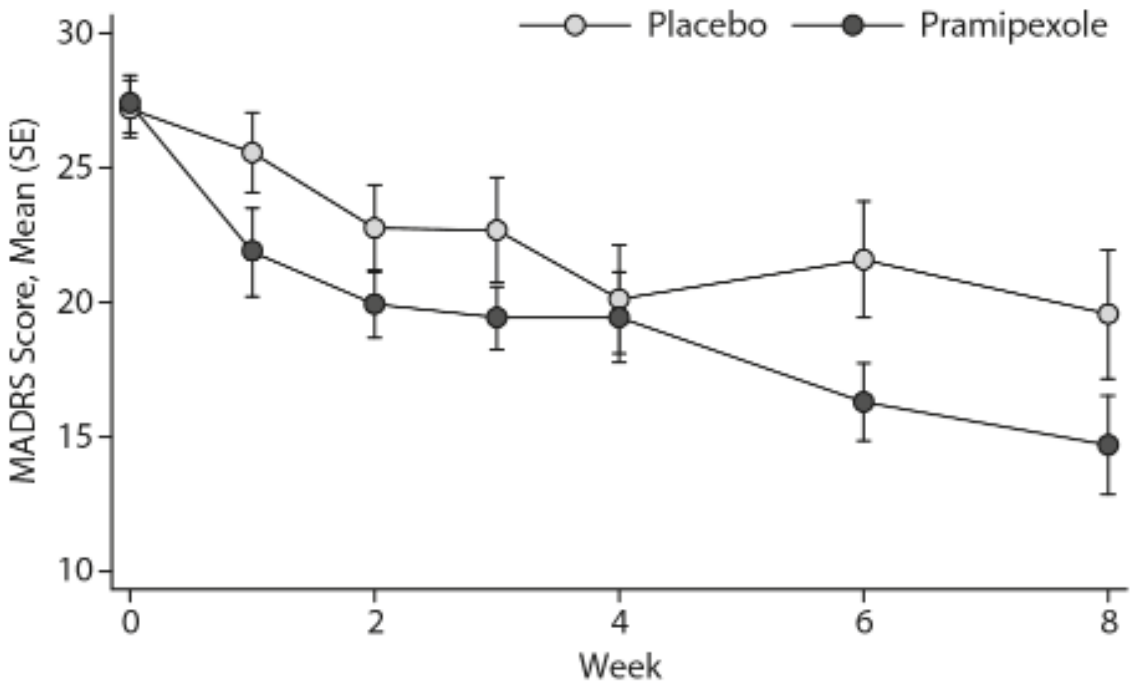


FIGURE 1. Placebo-subtracted mean change in HAMD-28 total score (–2.11 ± 1.01 vs –1.0 ± 0.60, p = 0.34) in atypical versus nonatypical subtypes treated with STS. Abbreviations: HAMD, Hamilton Depression Rating Scale; STS, selegiline transdermal system.

Pramipexol augmentation in TRD

Cusin et al. 2013 (n = 60)

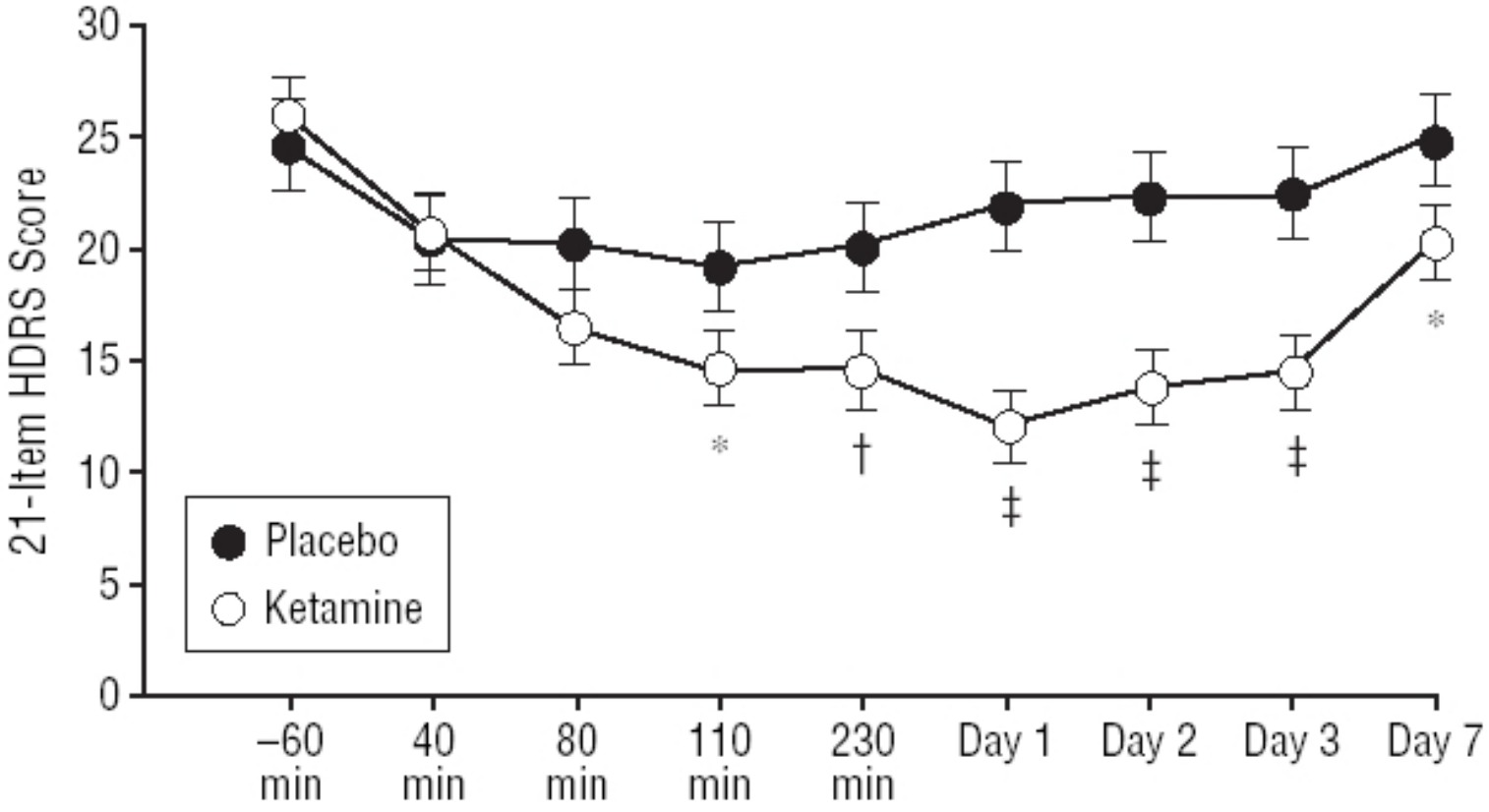
Figure 1. Mixed-Effects Linear Regression Analysis of Montgomery-Asberg Depression Rating Scale (MADRS) Scores Over Time, by Treatment Group



Response – 40% vs 27%
Remission – 33% vs 23%

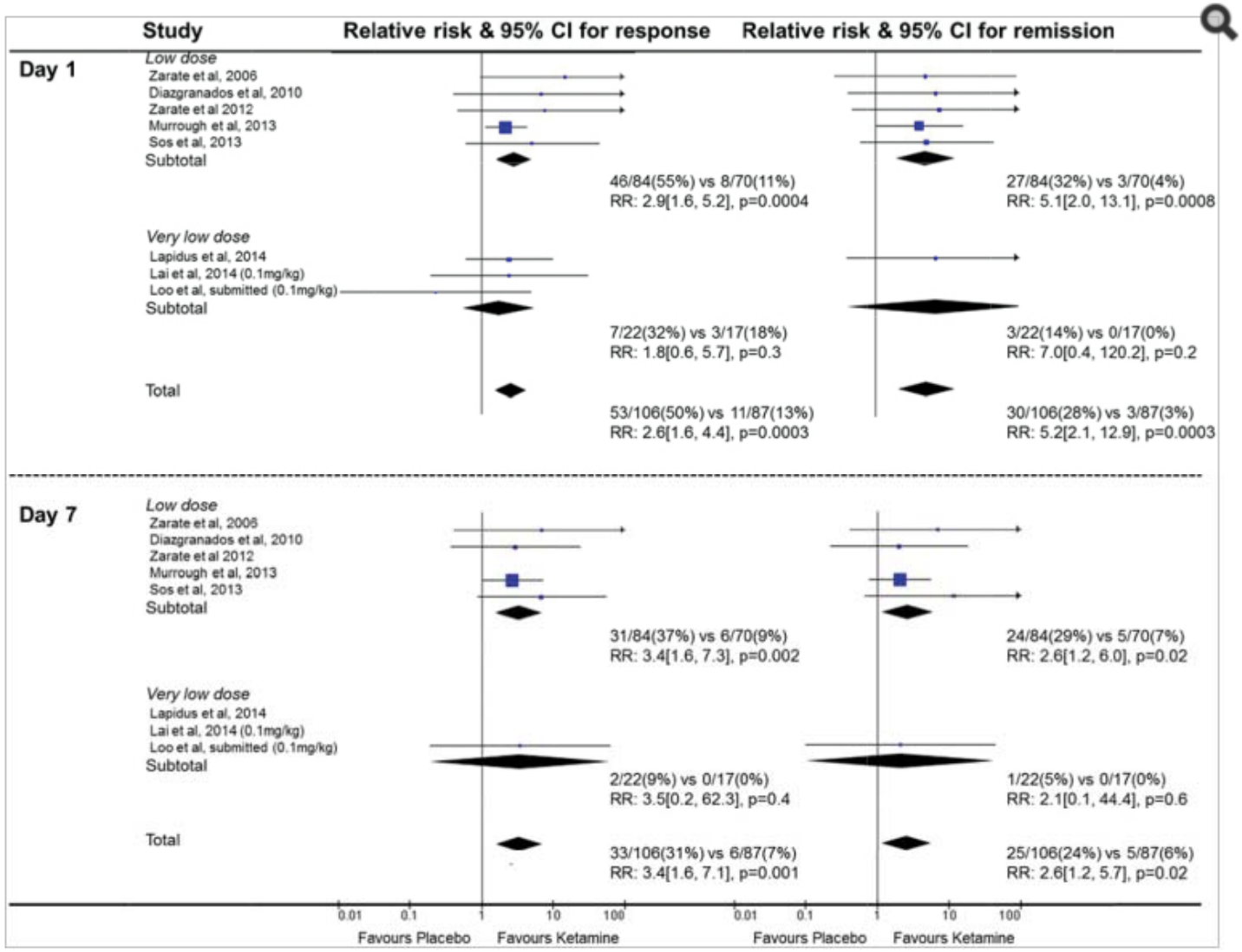
Dose:
Start at 0.25mg bd
Increase by 0.25mg bd weekly
Target 1.5mg bd
Mean = 1.35mg/day

Single dose of ketamine in TRD



Zarate et al 2006

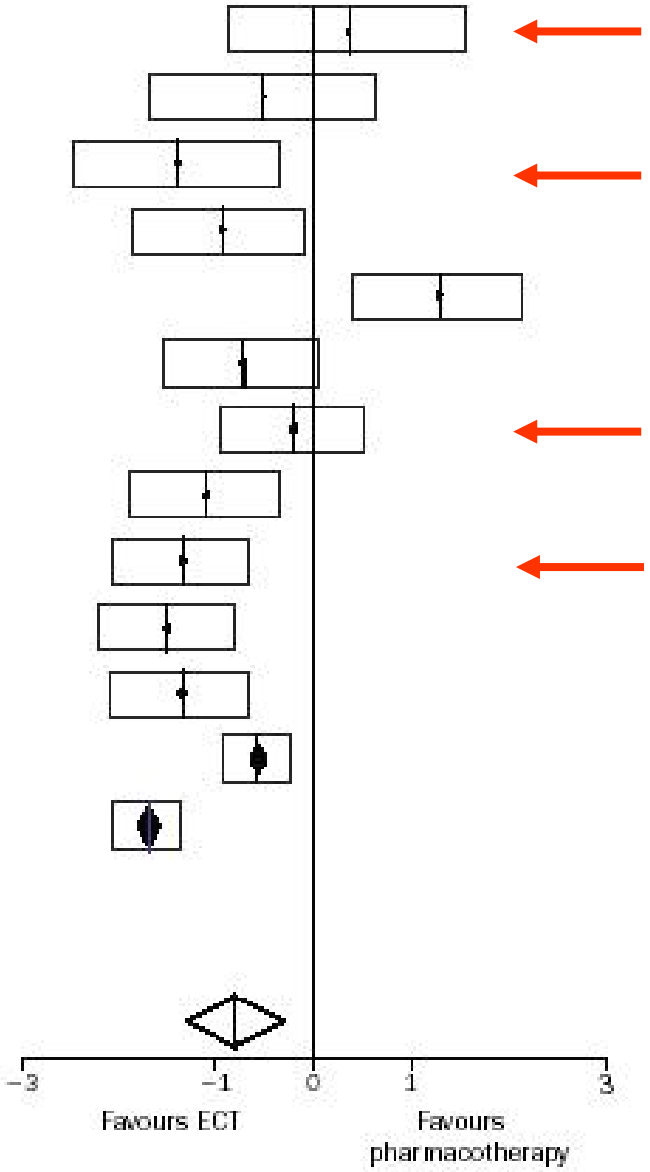
Single dose of ketamine: Metanalysis



Xu et al. 2016

ECT vs Pharmacotherapy

Trial*	Number of participants	Standardised effect size (95% CI)
Steiner 1978[16]	12	0·369 (–0·840 to 1·578)
Wilson 1963[10]	12	–0·513 (–1·663 to 0·637)
Davidson 1978[17]	19	–1·389 (–2·449 to –0·328)
McDonald 1966[18]	22	–0·930 (–1·813 to –0·047)
Gangadhar 1982[19]	32	1·287 (0·406 to 2·169)
MacSweeney 1975[20]	27	–0·714 (–1·492 to 0·065)
Dinan 1989[21]	30	–0·196 (–0·926 to 0·534)
Janakiramaiah 2000[22]	30	–1·095 (–1·863 to –0·328)
Folkerts 1997[23]	40	–1·336 (–2·032 to –0·640)
Herrington 1974[24]	43	–1·497 (–2·174 to –0·821)
Stanley 1962[25]	47	–1·342 (–2·047 to –0·638)
Medical Research Council 1965[26]	204	–0·559 (–0·883 to –0·234)
Greenblatt 1964[27]	242	–1·683 (–2·020 to –1·346)
Pooled fixed effects		–1·010 (–1·170 to –0·856)
Pooled random effects		–0·802 (–1·290 to –0·289)



UK ECT Review Group 2003

NCMD
Northern Centre for Mood Disorders

rTMS

Newcastle University
Institute of Neuroscience

Clinical Practice & Epidemiology in Mental Health, 2011, *7*, 167-177

Open Access

Meta-Review of Metanalytic Studies with Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Major Depression

Bernardo Dell'Osso*, Giulia Camuri, Filippo Castellano, Vittoria Vecchi, Matteo Benedetti, Sara Bortolussi and A. Carlo Altamura

Department of Psychiatry, University of Milan, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano, Italy

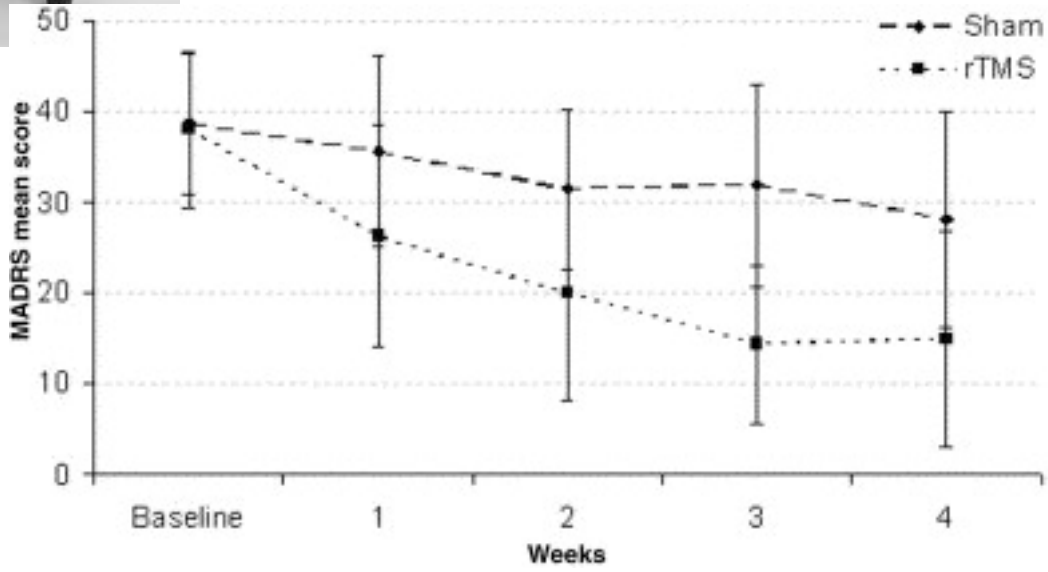
Abstract: *Background:* Major Depression (MD) and treatment-resistant depression (TRD) are worldwide leading causes of disability and therapeutic strategies for these impairing and prevalent conditions include pharmacological augmentation strategies and brain stimulation techniques. In this perspective, repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique with a favorable profile of tolerability which, despite being recently approved by

stimulation. *Results:* First meta-analyses on the efficacy of rTMS for the treatment of MD and TRD have shown mixed results. On the other hand, more recent meta-analytic studies seem to support the antidepressant efficacy of the technique to a greater extent, also in light of longer periods of stimulation (e.g. > 2 weeks). *Conclusion:* rTMS seems to be an effective and safe brain stimulation technique for the treatment of medication refractory depression. Nevertheless, further studies are needed to better define specific stimulation-related issues, such as duration of treatment as well as durability of effects and predictors of response.

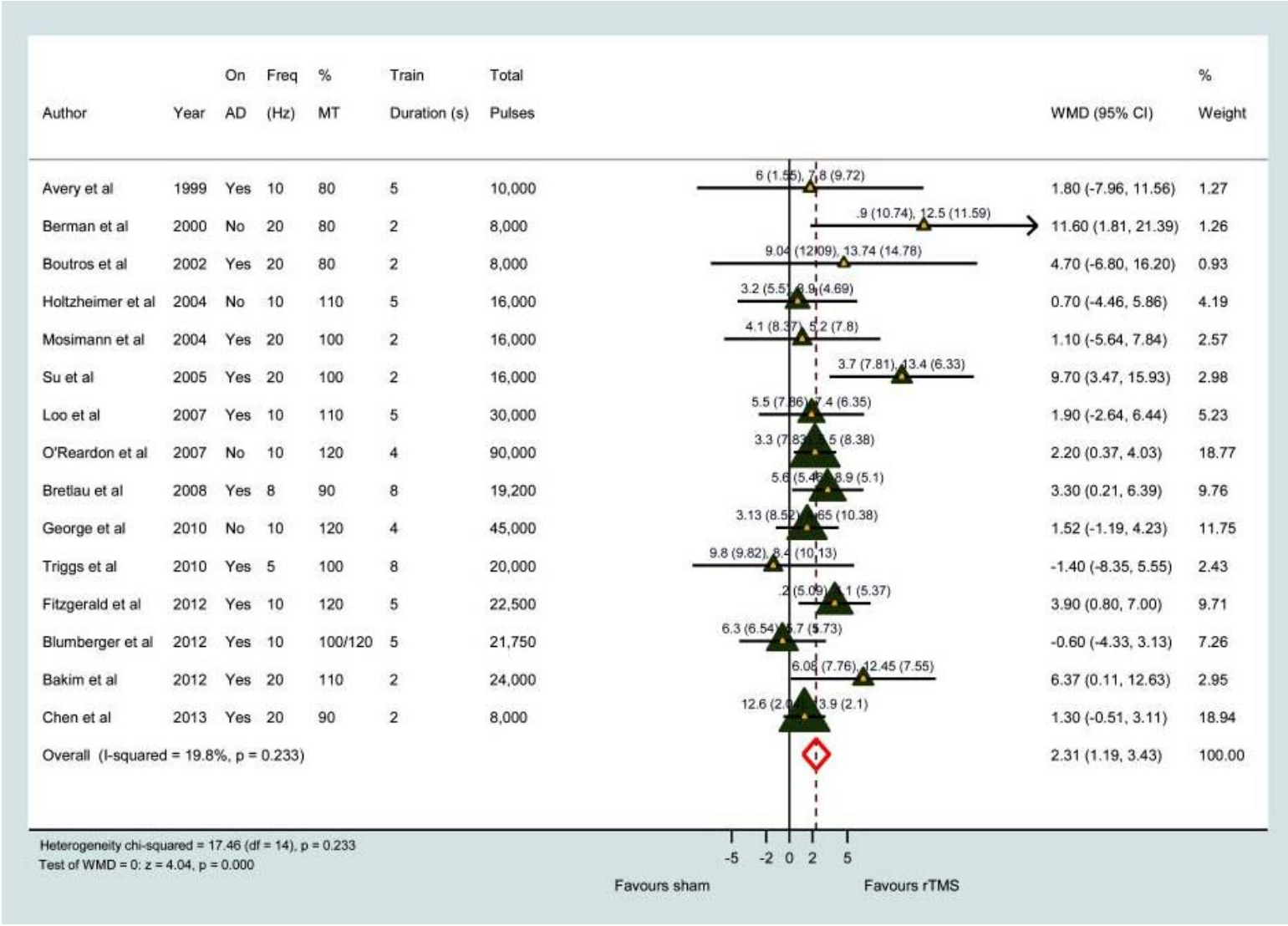
effective and safe brain stimulation technique for the treatment of medication refractory depression. Nevertheless, further studies are needed to better define specific stimulation-related issues, such as duration of treatment as well as durability of effects and predictors of response.

rTMS

Change in MADRS scores in patients with severe depression currently in amitriptyline (n= 46) Rumi et al. 2005

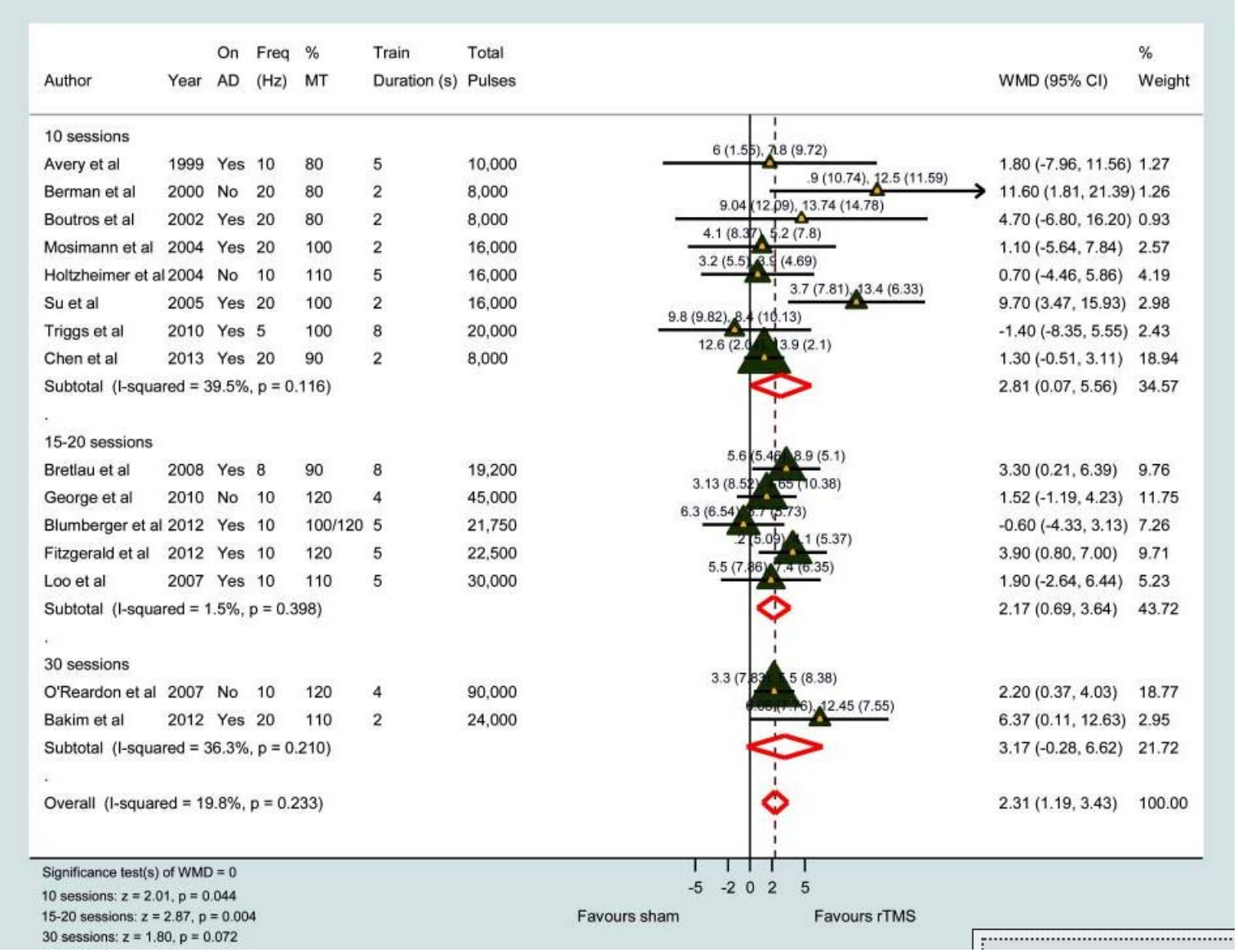


rTMS



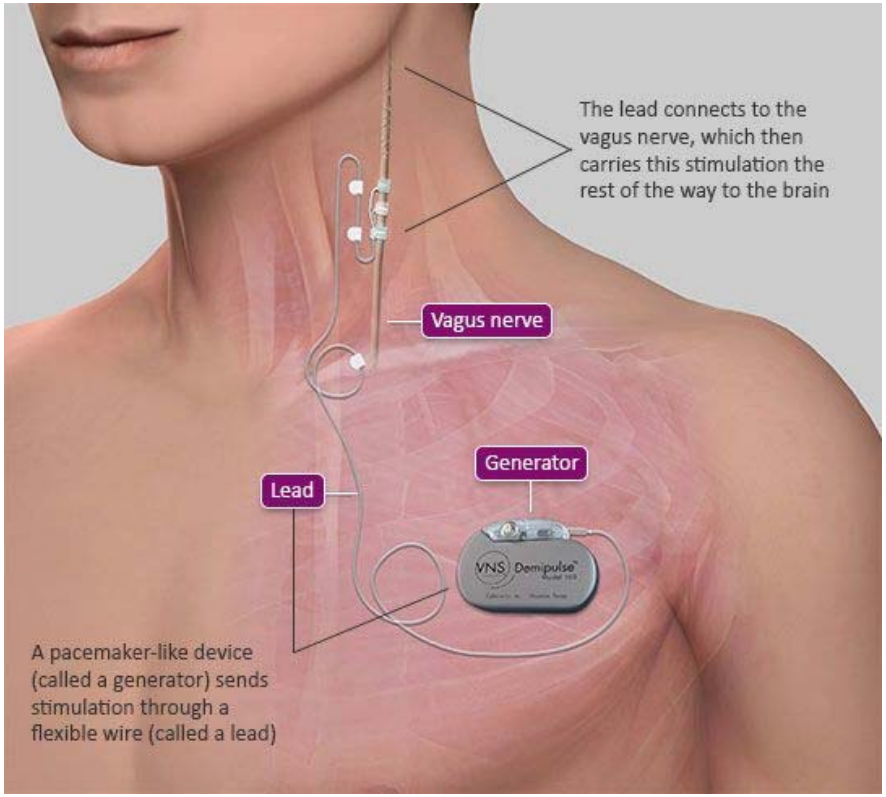
Health Quality Ontario, 2016

rTMS



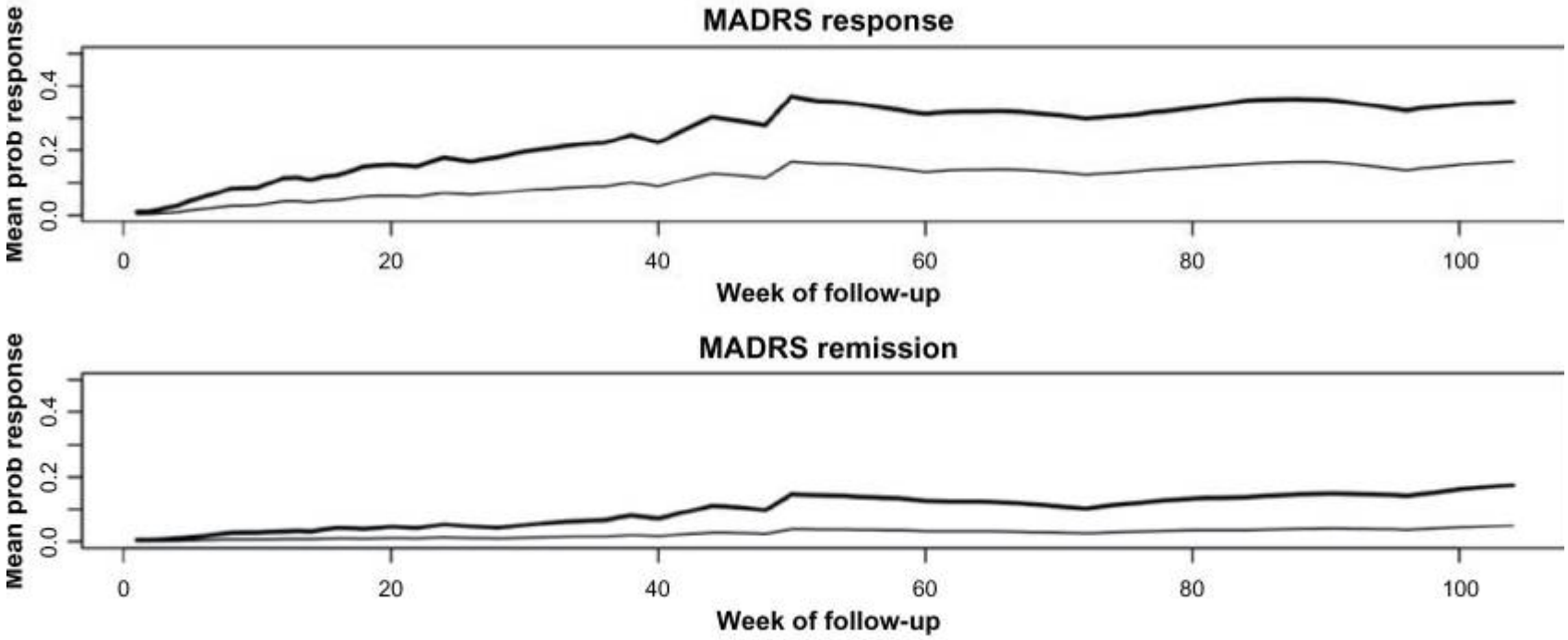
Health Quality Ontario, 2016

VNS


The lead connects to the vagus nerve, which then carries this stimulation the rest of the way to the brain
Vagus nerve
Generator
Lead
VNS Dem·pulse
A pacemaker-like device (called a generator) sends stimulation through a flexible wire (called a lead)

VNS

- Meta-analysis of non-randomised longitudinal studies (Berry et al. 2013)
- 96 weeks of treatment with VNS + TAU (n = 1035) versus TAU (n = 425)

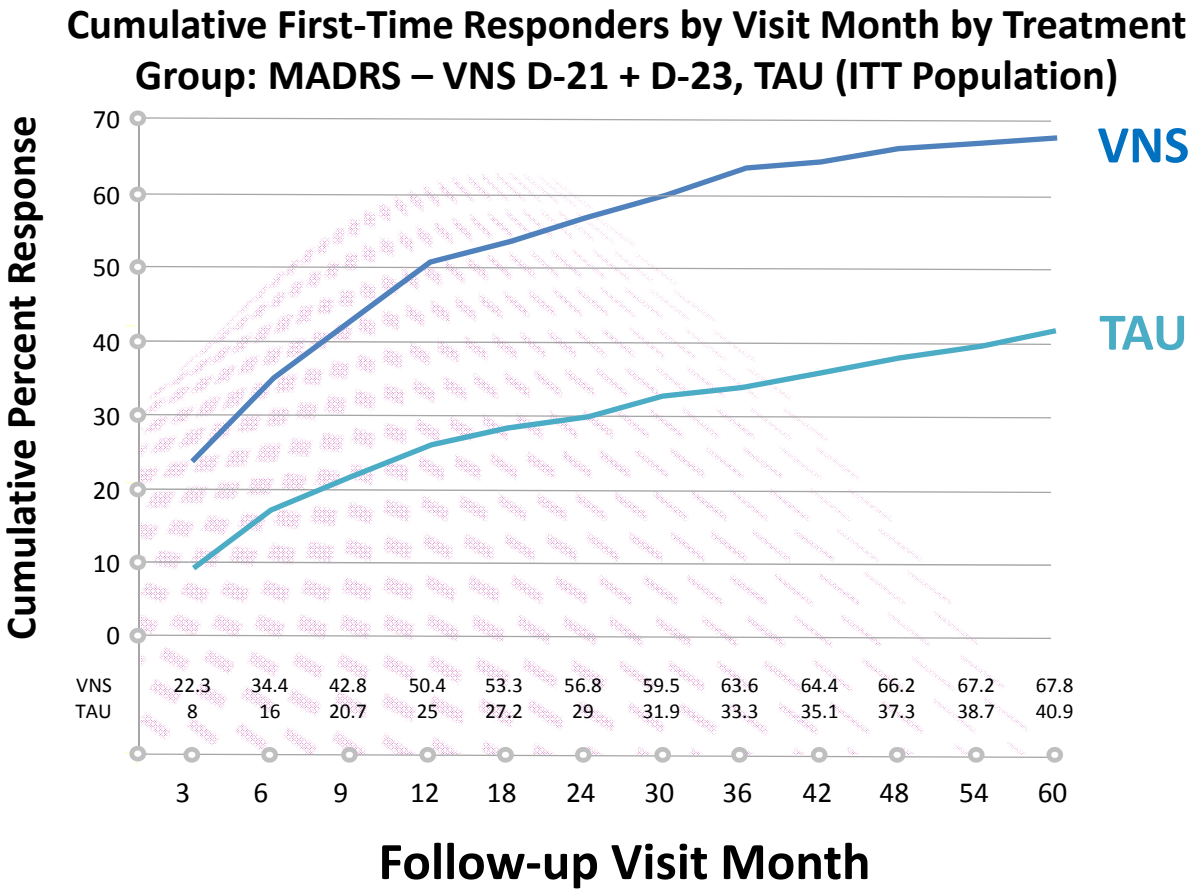


Response rate				
weeks	12	24	48	96
VNS + TAU	12%	18%	28%	32%
TAU	4%	7%	12%	14%

Remission rate				
weeks	12	24	48	96
VNS + TAU	3%	5%	10%	14%
TAU	1%	1%	2%	4%

VNS: LivaNova Registry data (in Press in Am J Psych)

Primary Endpoint – **Response Rate** based on MADRS



Cumulative Response Rate at 5 years

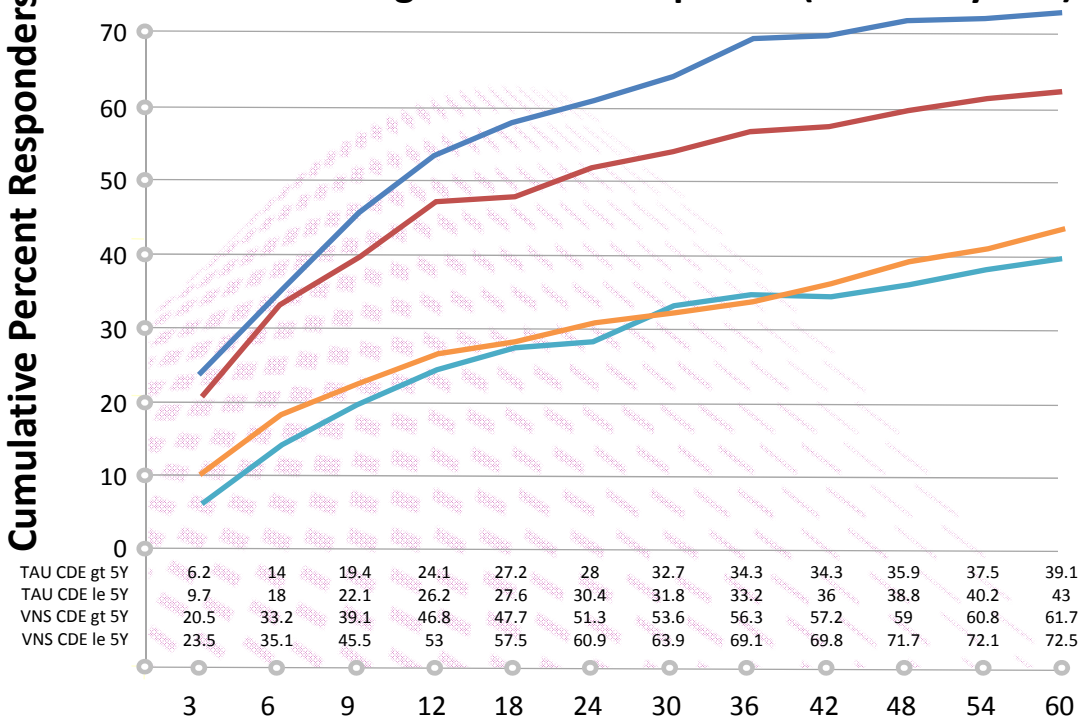
67.8% for VNS Therapy
vs. 40.9%
for TAU (P<0.001)
(NNT=4)

Data provided by LivaNova

VNS: LivaNova Registry data (in Press in Am J Psych)

Exploratory Analysis – **Response** based on MADRS

Cumulative First-Time Response by Visit Month by Treatment Group: MADRS – VNS D21+D23 vs. TAU (ITT Population) based on Length of Current Episode (<5 or >5 years)



Cumulative Response Rate Based on Length of Current MDE (5 year Threshold) at 5 Years

VNS (<5 yrs)(n=194) 72.5%

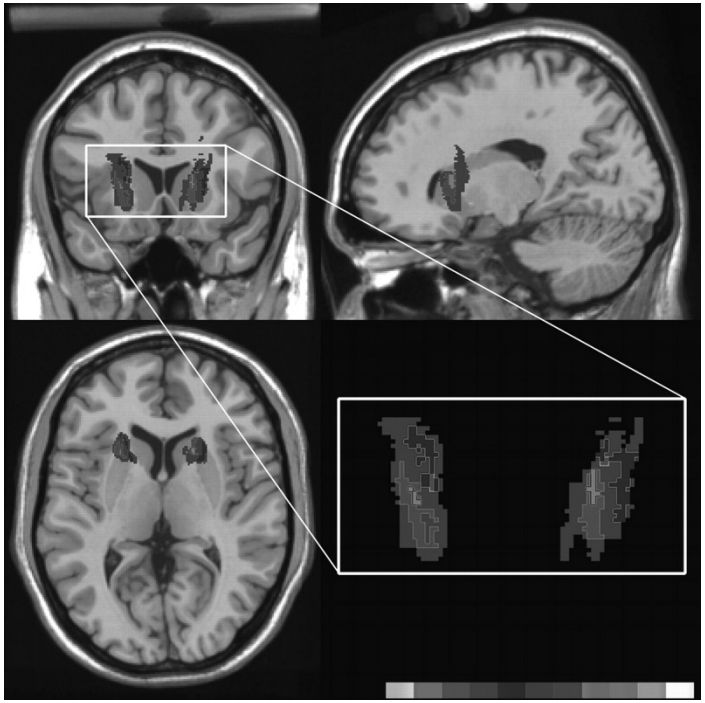
TAU (<5 yrs) (n=62) 43.0%

VNS (≥ 5yrs) (n=136) 61.7%

TAU (≥ 5yrs) (n=50) 39.1%

Data provided by LivaNova

Anterior cingulotomy



Comparison of lesions (overlaid as regions of interest) for responders (n=4 –lighter grey) and non-responders (n=6 – darker grey).

Table 4 Changes in rating scales following anterior capsulotomy (n=20)

Rating scale	Baseline	Postop	12 months	Long term follow-up	Percentage change at long term	p Value (baseline to long term)
HRSD-17 (actual scores)	26.8±3.9 (n=6)	20.8±10.6 (n=4)	15.3±10.7 (n=6)	13.3±12.0 (n=18)	−50.7	0.101 (n=6)
HRSD-17 (imputed scores)	23.3±4.6 (n=18)	15.8±7.0 (n=16)	16.2±7.0 (n=12)	13.8±11.6 (n=20)*	−44.2	0.004 (n=18)
MADRS (not imputed)	39.6±6.5 (n=18)	24.2±11.6 (n=16)	24.1±12.2 (n=12)	22.6±16.4 (n=20)	−42.9	0.001 (n=18)
LQoLP (mean satisfaction scores)	3.9±1.1 (n=12)	N/A	4.5±0.92 (n=7)	4.9±0.9 (n=17)	+25.6	0.049 (n=11)
HADS (anxiety subscale)	14.7±5.0 (n=10)	8.5±6.9 (n=6)	8.4±8.0 (n=5)	10.4±4.9 (n=17)	−29.3	0.132 (n=9)

*Data not imputed at long term follow-up.
Paired samples t-test used to calculate p values.
HADS, Hospital Anxiety and Depression Scale; HRSD, Hamilton Rating Scale for Depression; LQoLP, Lancashire Quality of Life Profile; MADRS, Montgomery Asperg Depression Rating Scale.

David Christmas et al. J Neurol Neurosurg Psychiatry 2011;82:594-600

Preserving hope

- What do you do if you have exhausted all options included in the guidelines for routine use?
- Is it sensible to keep trying endless trials of serotonergic/noradrenergic treatments?
- What other treatment options are available?
- When should such treatments (and/or referral to specialist services) be considered?

What threshold should be used to consider non-standard treatments? "Treatment resistant depression"- a concept that has had its time

- There is no consistent definition of TRD
  - Most commonly failure to respond to two adequate courses of different antidepressants
  - Utility as the point of referral from primary into secondary care?
- However there are a number of issues with the definition
  - No good evidence of qualitative difference in demographics, clinical characteristics or biological measures in patients with and without TRD
  - Lack of tolerability is usually not considered
  - Non-sustained response is not considered
  - Usually only medication is considered in the definition
  - Unclear if this relates to all major depressive episodes (MDE)
  - Limited clinical utility
    - NICE recommendations for referral to secondary care not based on number of treatment failures

The need for an additional or alternative threshold

- There is an expanding number of highly specialised treatments for patients with resistant depression
  - Augmentation strategies that BAP recommends for "specialist centres"
  - Expensive drug options e.g. transdermal selegiline
  - Controversial treatments e.g. maintenance ECT
  - Other physical non-drug treatments e.g. VNS and ablative neurosurgery
- When should a patient be considered suitable for consideration of such options??

  (the concern is that currently such options are not considered at all)

"Multi-therapy resistant-major depressive disorder" (MTR-MDD)

- Concept based on consensus group views
  - Publication under review
- Higher threshold than traditional TRD
- Specific to MDD (MTR-BD criteria being worked on)
- Takes into account
  - Multiple therapies (drugs, psychotherapy, ECT)
  - Intolerance
  - Non-sustained response
- Aim to identify as early as possible the point where further trials of "standard" (mainly monoaminergic) treatments are likely to be of limited benefit
  - i.e the point in time when "non-standard" treatments **should be considered.**
  - The actual point at which different "non-standard" treatments are used is likely to be different between different treatments

Proposed MTR-MDD Criteria

Episode of MDD of at least moderate severity for ≥2 years or ≥3 documented episodes of moderate-to-severe depression (DSM-5 criteria)	
Since the last period of recovery (defined as remission for at least 12 months), or since illness onset if there has been no period of recovery, there has been a failure of the following interventions to lead to a response, maintain a response, or be tolerated: **(Note that interventions from (a), (b) and (c) may have occurred concurrently)**	(a) A substantial trial (e.g. at least 16 hours) of a structured, evidence-supported psychological therapy. Ideally there should have been at least 1 trial in combination with pharmacotherapy.
	(b) 4 adequate trials of antidepressants (at least 1 from at least 3 classes): i) 5-HT reuptake inhibitors (e.g. SSRIs, clomipramine) ii) NA reuptake inhibitors (e.g. reboxetine, lofepramine, nortriptyline) iii) 5-HT & NA reuptake inhibitors (e.g. SNRIs, amitriptyline, imipramine) iv) MAOI (e.g. phenelzine, moclobemide) v) Others (e.g. mirtazapine, vortioxetine, agomelatine, bupropion)
	(c) At least 2 adequate trials of different evidence based augmentation/combination agents: i) Atypical antipsychotics (aripiprazole or quetiapine are preferred) ii) Lithium (ideally with a plasma level of 0.6 – 1.0 mmol/l) iii) Tri-iodothyronine
	(d) A trial of ECT (at least 8 treatments, and ideally bilateral if tolerated). The requirement for a course of ECT may be waived if there is a recognised contraindication to ECT or the patient has, despite extensive discussions and the provision of information, declined a trial of ECT, or there have been well-documented adverse effects that have limited tolerability.

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Conclusions

- It is easy to fall into the trap of therapeutic nihilism when managing depression
- Hope can be maintained by remembering the rapidly expanding number of treatment options for MDD
- However, the use of many of these options is likely to be primarily in specialist centers
- MTR-MDD criteria provides:
  - A prompt for consideration of what conventional treatments should be considered
  - a threshold for consideration of possible use of non-standard therapies and/or referral

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  - Tertiary care, Dundee
- Tony Cleare
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- Lisa Insole
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- Mari McGeever
  - Primary Care, Newcastle
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- Lucy Robinson
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  - Tertiary care, London
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