Medicine

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Monoamine oxidase inhibitors (MAOIs): *not to be forgotten?*

David S Baldwin, *Professor of Psychiatry*
Clinical and Experimental Sciences
Faculty of Medicine

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dsb1@soton.ac.uk

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Declaration of interests

- President-Elect, British Association for Psychopharmacology, 2020-2022
- Councillor, European College of Neuropsychopharmacology, 2019-2022
- Medical Patron, Anxiety UK, 2002 onwards
- Chair, Psychopharmacology Committee of Royal College of Psychiatrists, 2017-2020
- Clinical Advisor, National Clinical Audit of Anxiety and Depression, 2017-2020
- President, Depression Alliance, 1995-2001
- I have researched, prescribed and taken antidepressants
- I adhere to no particular ideology about the nature, causes or treatment of mental disorders

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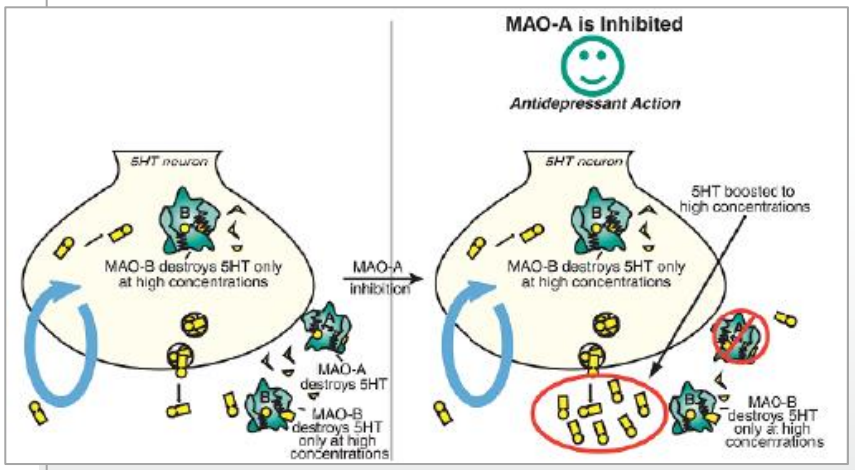
PS03/20

Use of monoamine oxidase inhibitors in psychiatric practice

Samuel R Chamberlain
Antonio Metastasio
Paul RA Stokes
David S Baldwin

July 2020



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Redundant - or neglected?

- POMH review of patient records from 55 mental health services (n=2082) indicates MAOIs were prescribed to less than 1% of patients [1]
- study in European tertiary psychiatric treatment centres found MAOIs were used as primary treatment in only 0.3% of patients with unipolar depression [2]
- MAOI prescription independently associated with remission at discharge and follow-up in inpatients with treatment-resistant depression [3]
- MAOIs are recommended as a potential treatment option in patients with refractory depression in NICE and BAP guidelines [4, 5]
- low use of MAOIs probably reflects widespread lack of familiarity and concerns about potential adverse effects [6]

1. Paton C et al. Ther Adv Psychopharmacol 2020; 10. doi:10.1177
2. Dold M et al. Eur Neuropsychopharmacol 2016; 26: 1960-1971
3. Fekadu A et al. Br J Psychiatry 2012; 201: 369-375
4. National Institute for Health and Care Excellence. Clinical Guideline CG90
5. Cleare A et al. J Psychopharmacol 2015; 29: 459-525
6. Menkes D et al. Austral Psychiatry 2016; 24: 371-373

'Atypical' depression : specified features

A. mood reactivity (i.e. mood brightens in response to actual or potential positive events)

B. two or more of the following features:

   1. significant weight gain or increase in appetite
   2. hypersomnia (at least 10 hrs/day or 2 hrs more than when not depressed)
   3. leaden paralysis (i.e. heavy, leaden feelings in arms or legs, for at least an hour per day)
   4. long-standing pattern of interpersonal rejection sensitivity (not limited to episodes of mood disturbance) that results in significant social or occupational impairment: trait with early onset and persists throughout most of adult life

C. criteria are not met for melancholic or catatonic features

American Psychiatric Association (2013). *Desk Reference to Diagnostic Criteria from DSM-5* ™

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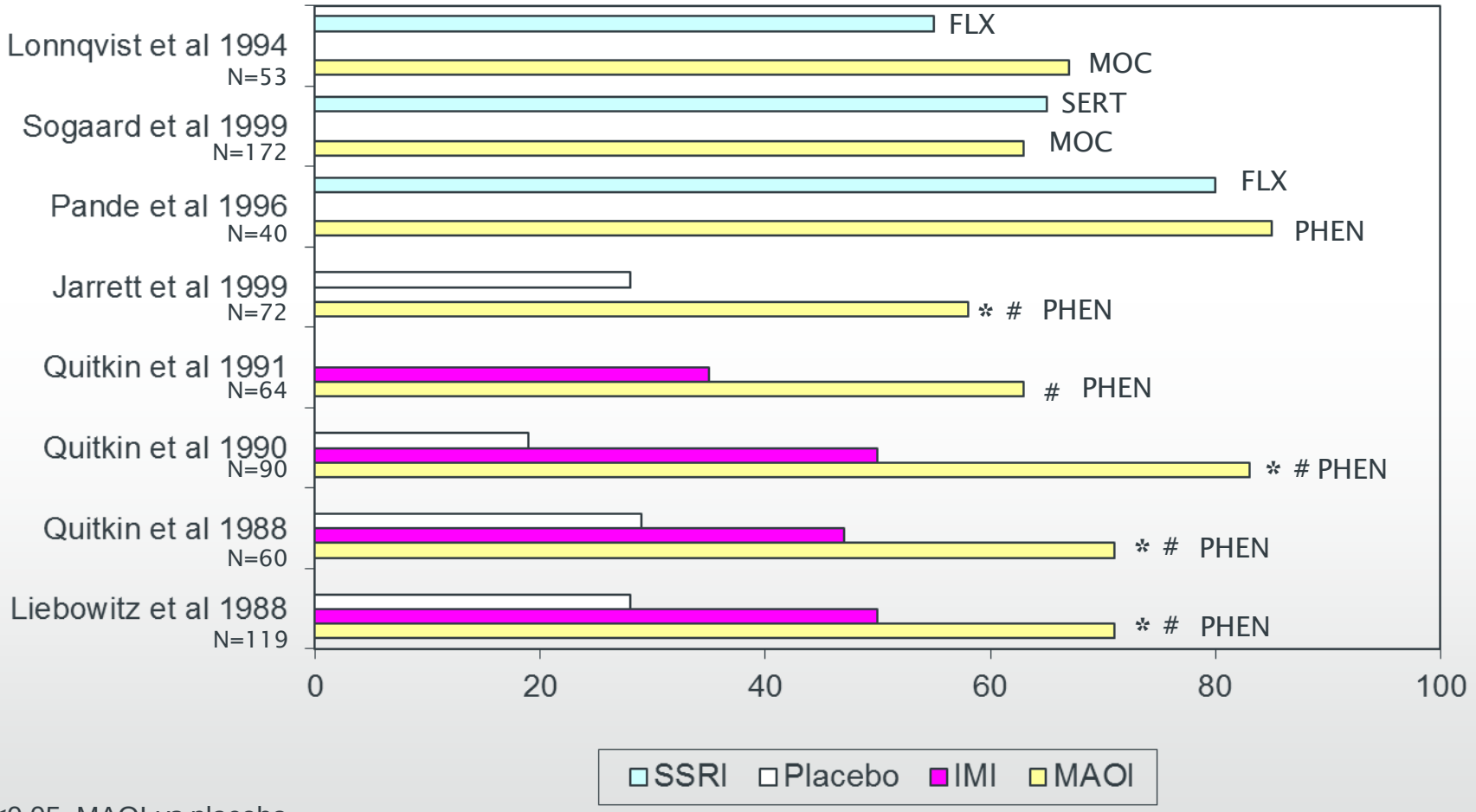
‘Atypical’ depression: response rates



* p<0.05, MAOI *vs* placebo

# p <0.05, MAOI *vs* TCA

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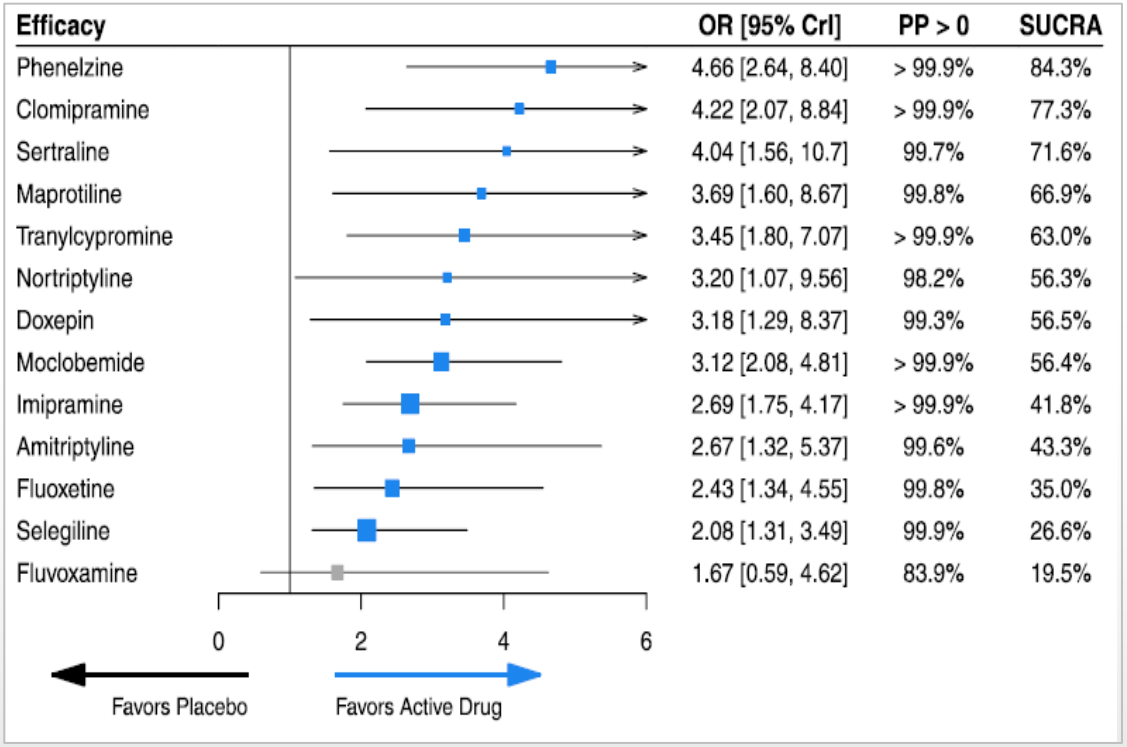
Comparative efficacy in depressive disorders



- systematic review and network meta-analysis
- 52 double-blind randomised placebo-controlled trials
- 14 antidepressants, N=6462
- phenelzine superior when compared to all other antidepressants
- no different to placebo in all-cause drop-outs

'… re-evaluation of the use of MAOI as antidepressant agents is necessary…'

Suchting R et al. J Affect Disord 2021; 282: 1153-1161

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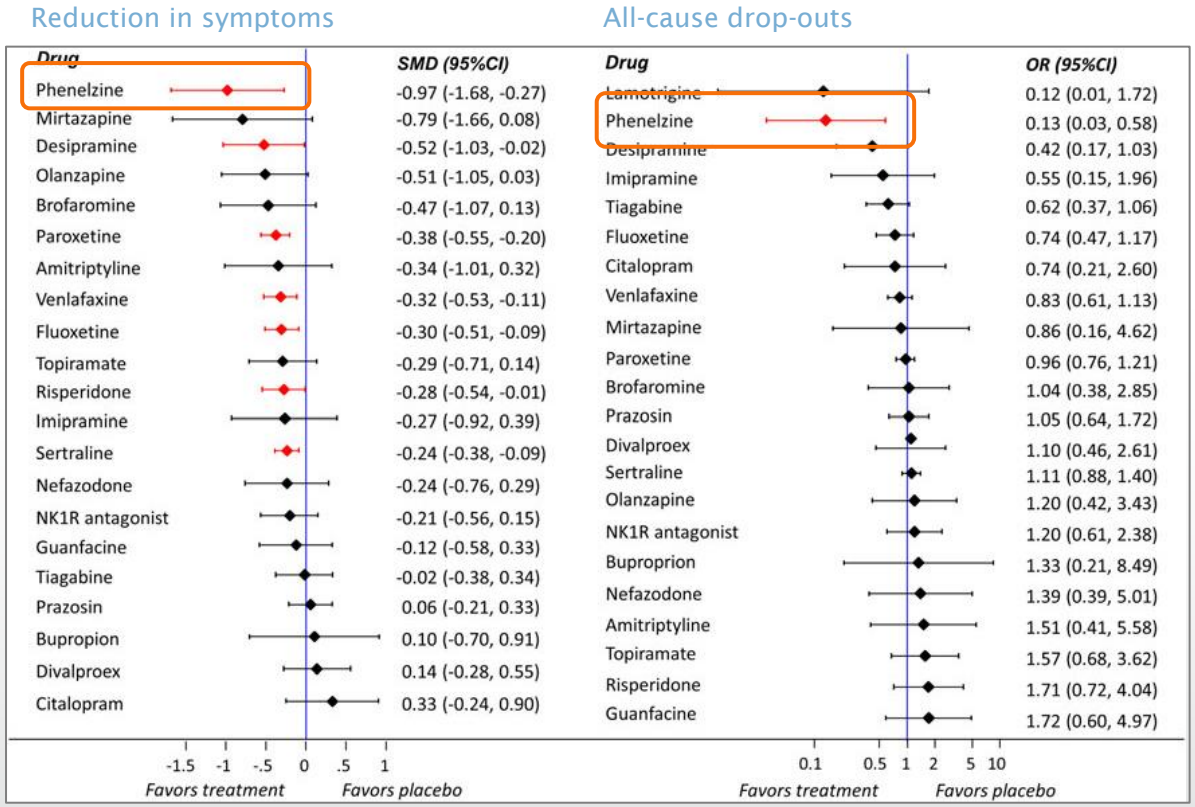
Pharmacological treatment of PTSD

- network meta-analysis: 51 double-blind RCTs, 25 interventions, 6189 patients
- phenelzine superior to many other drugs (and only drug superior to placebo in terms of drop-outs)
- '...probably not robust enough to suggest phenelzine as a drug of choice'
- '...findings from this review reinforce the idea that phenelzine should be prioritized in future trials...'



Cipriani A et al. Psychol Med 2017; 48: 1975-1984

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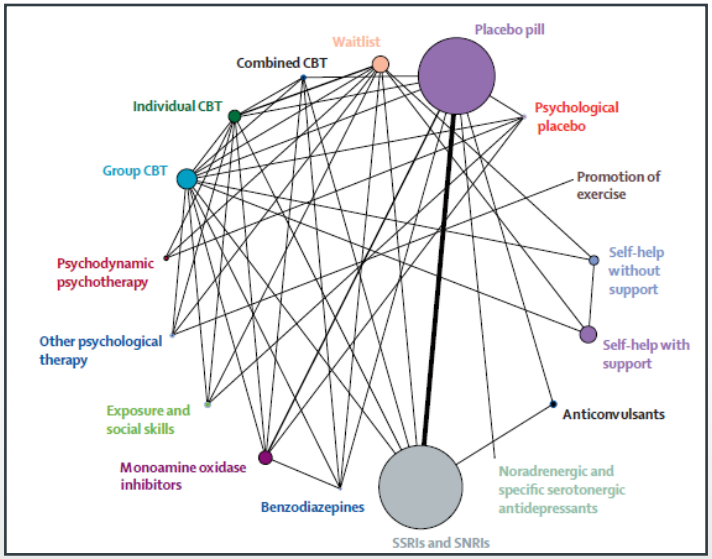
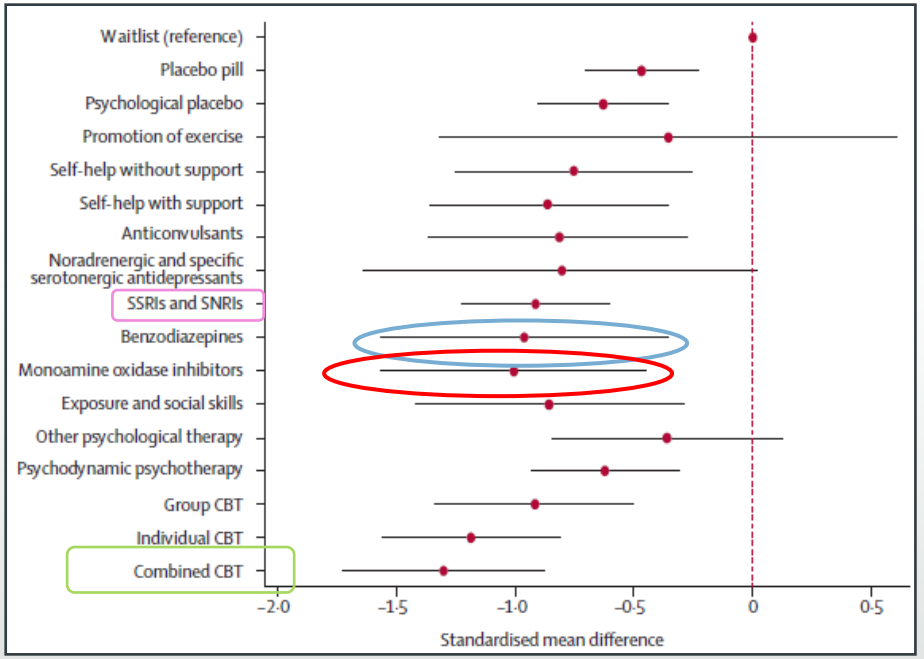
Social anxiety disorder: network meta-analysis

- network meta-analysis of 101 trials (13,164 patients) of 41 interventions
- SSRI and SNRI superior to pill placebo, CBT superior to psychological placebo – but:

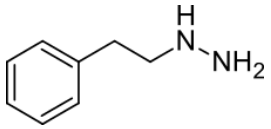




- largest effects were for MAOIs (SMD -1.01) and benzodiazepines (SMD -0.96)
- larger effect size for phenelzine (-1.28) than moclobemide (-0.74)

Mayo-Wilson E et al. Lancet 2014; 1: 368-376

Phenelzine



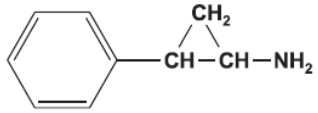
- non-selective and irreversible inhibitor of monoamine oxidase
- prevents breakdown of neurotransmitters 5-HT, A, NA, DA (and melatonin)
- also prevents breakdown of 'trace amine neuromodulators' (phenylethylamine, tyramine etc.)
- metabolite (PEH) inhibits GABA-transaminase and increases GABA levels
- hypertensive reaction possible with tyramine-containing foods + cough/cold medicines
- risk of serotonin syndrome if combined with SSRI, SNRI, serotonin agonists/releasers
- efficacious in unipolar, bipolar depression and dysthymia
- doses may need to be as high as 90 mg/day to achieve necessary level of MAO inhibition
- probably less effective than tricyclic antidepressants in severely depressed inpatients
- possible superiority in atypical depression?
- efficacious in panic disorder, social phobia, PTSD, bulimia
- potential repurposing in prostate cancer (as disrupts androgen receptor signalling)

Tolerability profile of phenelzine

- early recognition of high incidence of dizziness and hypotension [1]
- severe hypertensive reaction first described after few years [2]
- overall tolerability comparable to that with tricyclic antidepressants [3]
- longer-term tolerability in persistent depression (MAOIs) comparable to SSRIs [4]
- periodic reports of hepatoxicity [5] and vitamin B6 (pyridoxine) deficiency [6]

1. Davies G. BMJ 1960; 2 (5204): 1019
2. MacLeod I. BMJ 1965; 1 (5449): 1554
3. Thase M et al. Neuropsychopharmacol 1995; 12: 185-219
4. Meister R et al. PLoS One 201611(5):e0153380. doi: 10.1371
5. Rabkin J et al. J Clin Psychopharmacol 1985; 5: 2-9
6. Stewart JW et al. J Clin Psychopharmacol 1984; 4: 225-226

Tranylcypromine



- non-selective and irreversible inhibitor of monoamine oxidase
- 'substituted amphetamine' (but low potency as dopamine releasing agent)
- noradrenaline reuptake inhibitory properties at higher doses (40/60 mg/day)[1]
- comparable efficacy to other antidepressants in (non-treatment-resistant) depression [2]
- efficacy in treatment-resistant depression (following TCA and SSRI): response rate 58.1% [2]
- but lower response rate in STAR*D: 12.1% response *vs.* 24% for [VEN+MIRT] [3]
- potential repurposing in acute myeloid leukaemia (can induce myeloid differentiation)

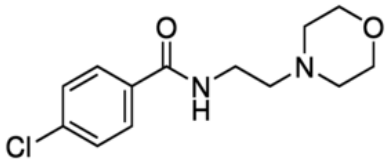
1. Ulrich S et al. Eur Neuropsychopharmacol 2017; 27: 697-713
2. Ricken R et al. Eur Neuropsychopharmacol 2017; 27: 714-731
3. McGrath PJ et al. Am J Psychiatry 2006; 163: 1531-1541

Tolerability profile of tranylcypromine

- MAOI at 10-20 mg/day, NRI at 40-60 mg/day, DA-releaser at ~ 100 mg/day [1]
- optimal response obtained in patients who can tolerate 40-60 mg/day [2]
- 'dizziness' relating to postural hypotension is most common reason for stopping
- common adverse effects include insomnia, increased anxiety, agitation, dry mouth
- weight gain, sexual dysfunction infrequent
- tyramine-restricted diet is essential
- risk of severe cerebrovascular events estimated at 0.0014-0.007% [3, 4, 5]

1. Ricken R et al. Eur Neuropsychopharmacol 2017; 27: 714-731
2. Thase M et al. Neuropsychopharmacol 1995; 12: 185-219
3. Pare CM. Br J Psychiatry 1985; 146: 576-584
4. Baldessarini 1996. *The Pharmacological Basis of Therapeutics*, McGraw Hill, New York, pp. 431-459
5. Haas HJ, Buhre HJ. Jatrosom Med Welt 1973, 24: 221-224

Moclobemide



- reversible inhibitor of monoamine oxidase-A (RIMA), inhibition lasts less than 24 hrs
- selective (300 mg dose inhibits 80% MAO-A and 30% MAO-B)
- MAO-occupancy is around 75% for doses around 300-600 mg/day
- potentiation of pressor effect of tyramine is ~ 12% that of irreversible MAOIs
- hypertensive reaction unlikely if taken with tyramine-containing foodstuffs [1]
- efficacious in unipolar, bipolar depression and dysthymia [2]
- comparable efficacy to imipramine and clomipramine in hospitalised patients [3]
- some evidence of dose-response relationship in severe depression [4]
- efficacious in social phobia [5], possible efficacy at higher dosage in panic disorder [6]
- helpful in smoking cessation, ADHD, fibromyalgia, migraine, tension headache

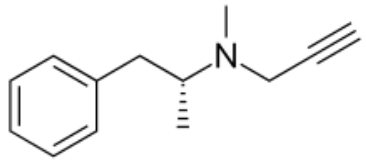
1. Baldwin DS, Rudge SE. Rev Contemp Pharmacother 1994; 5: 57-65
2. Bonet U. CNS Drug Reviews 2003; 9: 97-140
3. Angst J et al. J Clin Psychopharmacol 1995; 16S-23S
4. Lotufo-Neto F et al. Neuropsychopharmacol 1999; 20:226-247
5. Mayo-Wilson E et al. Lancet 2014; 1: 368-376
6. Uhlenhuth EH et al. J Clin Psychopharmacol 2002; 22: 275-284

Tolerability of moclobemide

- more common adverse effects include dizziness, nausea, insomnia [1]
- emergent sexual dysfunction less frequent (1.9%) than with SSRIs (21.6%) [2]
- animal models suggest potentiation of effects of pethidine [3]
- occasional reports of serotonin syndrome if combined with clomipramine [4] or SSRIs [5, 6] (but most cases occur following deliberate/inadvertent overdose)

1. Baldwin DS, Rudge SE. Rev Contemp Pharmacother 1994; 5: 57-65
2. Philipp M et al. Eur Neuropsychopharmacol 2000; 10: 305-314
3. Amrein R et al. Psychopharmacol 1992; 106: 24-31
4. Spigset O et al. BMJ 1993; 306: 248
5. Benazzi F. Pharmacopsychiatry 1996; 29: 162
6. Chan BSH et al. Med J Austral 1998; 169: 523-525

Selegiline (L-deprenyl)



- ‘selective’ but irreversible inhibitor of MAO-B (and MAO-A at high dosage)
- neuroprotective effects through inhibition of free radicals
- high affinity for sigma-1 receptors
- metabolites include levomethamphetamine and levoamphetamine
- delays need for and dosage of levodopa treatment in Parkinson’s disease
- risk of serotonin syndrome with SSRI and hypertensive reaction with tyramine
- transdermal patch licensed for treatment of major depressive disorder
- potential repurposing in melanoma (induces apoptotic cell death)

Transdermal selegiline in depression

- transdermal system increases bioavailability to 73% (from 4%)...
- ...but results in non-selective inhibition of MAO-A and MAO-B...
- ...although MAO-A in gastrointestinal tract is available to metabolize tyramine
- efficacious in both acute treatment [1, 2, 3] and in prevention of relapse [4]
- NNT for symptom reduction ~11, for remission ~9
- 3.6 times more likely to lead to remission than to drop-out due to adverse effects [5]
- no difference from placebo in weight gain or sexual dysfunction

1. Amsterdam J. J Clin Psychiatry 2003; 64: 208-214
2. Bodkin JA, Amsterdam JD. Am J Psychiatry 2002; 159: 1869–1875
3. Feiger A et al. J Clin Psychiatry 2006; 67: 1354–1361
4. Amsterdam JD, Bodkin JA. J Clin Psychopharmacol 2006; 26: 579–586
5. Citrome L et al. J Affect Disord 2013; 151: 409-417

Symptoms on and after stopping MAOIs

- early descriptions in case reports with tranylcypromine [1, 2], phenelzine [3]
- associated with longer duration of phenelzine treatment [4]
- includes anxiety, mania, delirium, psychotic symptoms, autonomic disturbance [5, 6]
- moclobemide withdrawal linked to rebound REM sleep [7], and flu-like symptoms [8]

1. Le Gassicke J. Lancet 1963; i, 270
2. Ben-Arie O, George GCW. Br J Psychiatry 1979; 135: 273-274
3. Pitt B. BMJ 1974; 2 (5914)332-333
4. Tyrer P. J Affect Disord 1984; 6: 1-7
5. Dilsaver SC. Acta Psychiatr Scand 1988; 1; 1-7
6. Gahr M et al. Pharmacopsychiatry 2013; 46: 123-129
7. Baldwin DS, Rudge SE. Rev Contemp Pharmacother 1994; 5: 57-65
8. Curtin F et al. J Psychopharmacol 2002; 16: 271-272

What if supplies are threatened?

- identify patients currently taking an MAOI (send to be ~ 800 on phenelzine)
- review within secondary care mental health services
- consider whether there is scope for planned gradual withdrawal of treatment
- consider switch from older MAOI to moclobemide
- consider switch to oral or (special, import) transdermal selegiline
- consider switch to other classes of antidepressant
- expect a bumpy course!

What if supplies are threatened?

- advise patients who stop phenelzine to continue their restricted diet (with avoidance of tyramine-containing foods and beverages) and their avoidance of some proprietary cough medicines for 2-3 weeks after treatment is withdrawn
- washout period of at least 2-3 weeks is always advised after phenelzine is stopped, before starting an alternate antidepressant
- if switching to another irreversible (e.g. tranylcypromine) or to a reversible (e.g. moclobemide) MAOI, ensure a 2-3 week wash-out between drugs
- be aware of potential drug-drug interactions arising from residual effects of phenelzine (for example 'serotonin syndrome'): treatments with serotonin reuptake inhibitory properties (mainly SSRIs and SNRIs but also clomipramine and some other drugs) should not be started during the 2-3 week washout period
- as features of serotonin syndrome can emerge even 10 weeks after an MAOI is stopped, introduction of medicines with serotonin-reuptake inhibitor properties should be conducted cautiously with careful monitoring

A future for MAOIs?

- potential repurposing in oncological applications [1]
- MAO inhibition is proven mechanism for antidepressant efficacy
- MAO-A +/or MAO-B inhibition in many plant-derived substituted flavonoids [2]
- MAOI have indirect neuroprotective properties due to inhibition of H_2O_2 and aldehyde release: individual drugs may also have direct neuroprotective effects [3]
- 'repurposing' of MAOIs into other areas of medicine might extend their continuing use in the original indications [4]
- they should not be forgotten….

1. Moreira-Silva F et al. Pharmaceutics 2020; 12: doi: 10.3390/pharmaceutics12050410
2. Dhiman P. Molecules 2019; 24: 418. doi: 10.3390/molecules24030418
3. Finberg JPM, Rabey JM. Frontiers Pharmacol 2016 (18 October). Doi:01.3389/fphar.2016.00340
4. Baldwin DS, Chamberlain S. CNS Drugs. Under review.