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
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
Use of monoamine oxidase inhibitors in psychiatric practice

Samuel R Chamberlain
Antonio Metastasio
Paul RA Stokes
David S Baldwin

July 2020
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.  


- study in European tertiary psychiatric treatment centres found MAOIs were used as primary treatment in only 0.3% of patients with unipolar depression.  


- MAOI prescription independently associated with remission at discharge and follow-up in inpatients with treatment-resistant depression.  


- MAOIs are recommended as a potential treatment option in patients with refractory depression in NICE and BAP guidelines.  


- low use of MAOIs probably reflects widespread lack of familiarity and concerns about potential adverse effects.  

‘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™
‘Atypical’ depression: response rates

- Lonnqvist et al 1994
  - N=53
- Sogaard et al 1999
  - N=172
- Pande et al 1996
  - N=40
- Jarrett et al 1999
  - N=72
- Quitkin et al 1991
  - N=64
- Quitkin et al 1990
  - N=90
- Quitkin et al 1988
  - N=60
- Liebowitz et al 1988
  - N=119

* p<0.05, MAOI vs placebo

# p <0.05, MAOI vs TCA
### 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**

#### Efficacy

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>OR [95% Crl]</th>
<th>PP &gt; 0</th>
<th>SUCRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenelzine</td>
<td>4.66 [2.64, 8.40]</td>
<td>&gt; 99.9%</td>
<td>84.3%</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>4.22 [2.07, 8.84]</td>
<td>&gt; 99.9%</td>
<td>77.3%</td>
</tr>
<tr>
<td>Sertraline</td>
<td>4.04 [1.56, 10.7]</td>
<td>99.7%</td>
<td>71.6%</td>
</tr>
<tr>
<td>Maprotiline</td>
<td>3.69 [1.60, 8.67]</td>
<td>99.8%</td>
<td>66.9%</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>3.45 [1.80, 7.07]</td>
<td>&gt; 99.9%</td>
<td>63.0%</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>3.20 [1.07, 9.56]</td>
<td>98.2%</td>
<td>56.3%</td>
</tr>
<tr>
<td>Doxepin</td>
<td>3.18 [1.29, 8.37]</td>
<td>99.3%</td>
<td>56.5%</td>
</tr>
<tr>
<td>Moclobemide</td>
<td>3.12 [2.08, 4.81]</td>
<td>&gt; 99.9%</td>
<td>56.4%</td>
</tr>
<tr>
<td>Imipramine</td>
<td>2.69 [1.75, 4.17]</td>
<td>&gt; 99.9%</td>
<td>41.8%</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>2.67 [1.32, 5.37]</td>
<td>99.6%</td>
<td>43.3%</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>2.43 [1.34, 4.55]</td>
<td>99.8%</td>
<td>35.0%</td>
</tr>
<tr>
<td>Selegiline</td>
<td>2.08 [1.31, 3.49]</td>
<td>99.9%</td>
<td>26.6%</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>1.67 [0.59, 4.62]</td>
<td>83.9%</td>
<td>19.5%</td>
</tr>
</tbody>
</table>

*Favors Placebo* *Favors Active Drug*

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‘... re-evaluation of the use of MAOI as antidepressant agents is necessary...’

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

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)

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
  
- severe hypertensive reaction first described after few years
  
- overall tolerability comparable to that with tricyclic antidepressants
  
- longer-term tolerability in persistent depression (MAOIs) comparable to SSRIs
  
- periodic reports of hepatotoxicity and vitamin B6 (pyridoxine) deficiency

1. Davies G. BMJ 1960; 2 (5204): 1019
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)
- comparable efficacy to other antidepressants in (non-treatment-resistant) depression
- efficacy in treatment-resistant depression (following TCA and SSRI): response rate 58.1%
- but lower response rate in STAR*D: 12.1% response vs. 24% for [VEN+MIRT]
- potential repurposing in acute myeloid leukaemia (can induce myeloid differentiation)

Tolerability profile of tranylcypromine

- MAOI at 10-20 mg/day, NRI at 40-60 mg/day, DA-releaser at ~ 100 mg/day

- optimal response obtained in patients who can tolerate 40-60 mg/day

- ‘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. Pare CM. Br J Psychiatry 1985; 146: 576-584
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
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
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

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
3. Pitt B. BMJ 1974; 2 (5914)332-333
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 selegilene
- 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.
- A 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
- MAO inhibition is proven mechanism for antidepressant efficacy
- MAO-A +/or MAO-B inhibition in many plant-derived substituted flavonoids
- MAOI have indirect neuroprotective properties due to inhibition of \( \text{H}_2\text{O}_2 \) and aldehyde release: individual drugs may also have direct neuroprotective effects
- ‘repurposing’ of MAOIs into other areas of medicine might extend their continuing use in the original indications
- they should not be forgotten....