DOPAMINERGIC TREATMENT OF TREATMENT REFRACTORY MOOD DISORDERS

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Conflicts:

More enjoyment than facts ...

...on Amazon!
Failed Remission and High Relapse Rates Are Common in Mood Disorders

**MAJOR DEPRESSION: STAR*D OUTCOMES:**
*Sequenced Treatment Alternatives to Relieve Depression (STAR*D) was a collaborative study on the treatment of depression, funded by the National Institute of Mental Health*

<table>
<thead>
<tr>
<th>Treatment step 1 – citalopram</th>
<th>36.8% remission</th>
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<tbody>
<tr>
<td>Overall Remission Rates steps 1-4</td>
<td>67%</td>
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<tr>
<td>Treatment Resistant</td>
<td>23% after four steps of treatment</td>
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**BUT**

<table>
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<tr>
<th>Four Month Recurrence rates step 1-4</th>
<th>40.2%-71%</th>
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<tbody>
<tr>
<td>Recovery rates</td>
<td>67% x 60% = 40.3% &quot;Recovered&quot; at 4 months</td>
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Recovery: no episode of depression for 6 months; recovery is a more reliable outcome than remission

Recurrence: an episode of MDD after six months – assumed to be a "new" episode.
What about Bipolar Depression?
Sienaert P., Bipolar Disorder 2013

Response: Best Data Quetiapine - Bipolar Depression 60% response - no follow up recovery data

Lithium, lamotrigine, olanzepine, olanzepine + fluoxetine combination – less favorable

Antidepressants – 25% six week response

Zarate et al: Ketamine 79% response same as placebo at 7 days

Frye et al: Modafinil remission 44% vs 23%, ES = .47

Goldberg et al (2004): pramipexole (1.7 mg) 67% response vs. 20% placebo (p=.04)

Sienaert et al: ECT 64% moderate remission – no follow-up – (other studies relapse rates at least 50%)

Response to Dopaminergic Medications in Bipolar Depression
Dell’Osso et al, 2013

Usual NNT for psychiatric medications NNT 3-6
\[
\frac{100}{(\text{remission rate} - \text{placebo response})}
\]

Some Pramipexole (Goldberg TRMD, Zarate: close to NNT=2)

May be more effective in BPD than unipolar MDD

Dosage varies (from 1.0 mg -2.5 mg in these studies)
## Would Dopaminergic Medications Help?

<table>
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<tr>
<th>Bupropion</th>
<th>Aripiprazole (Abilify)</th>
<th>Modafinil</th>
<th>Stimulants</th>
<th>Pramipexole (PPX)</th>
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<tbody>
<tr>
<td>• Affinity for dopamine transporter&lt;br&gt;• Very weak - common use&lt;br&gt;• Two studies - did not exceed placebo when added to SSRIs</td>
<td>• Partial dopamine agonist – augments ADMs.</td>
<td>• Unknown full mechanism, some increase in dopaminergic function.</td>
<td>• Dextro-amphetamine, Methylphenidate – increase by surge</td>
<td>• D3 autoreceptor agonist – increases dopamine tonic levels.&lt;br&gt;• Was used in Parkinson's Disease for motor symptoms – 2% to loss of dopamine neurons.&lt;br&gt;• Was found to benefit depression (particularly anhedonia - inability to pursue and enjoy usual pleasures).&lt;br&gt;• Found effective in depression without Parkinson's Disease (Aiken C., 2007).&lt;br&gt;• PPX is off-patent (was Mirapex) – not marketed.</td>
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</table>

- Must be used carefully, dosed according to age (*older people seem to tolerate and require higher doses*).
- Can cause nausea, sleepiness, sex/gambling addiction.
- If stopped rapidly can cause DAWS (Dopamine Withdrawal Syndrome).

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### Levels of Treatment Resistance Operationally Defined

- **By number of adequately received treatments that failed to produce response or remission**
- **Treatment Refractory:**
  - SSRIs, SNRIs, TCAs, plus ECT (general considered ultimate) and sometimes MAOI – all failed to help patient.
  - Most studies consider definition to be failure to respond (remit) with two medications of differing mechanisms.
Case 1

JP

63 old male (first seen in 2003)
- with Treatment Resistant Chronic Depression since puberty
- retired early because of non-function secondary to depression

CLINICAL SYNDROME:
- chronic depressed mood-severe
- anhedonic
- decreased appetite
- absent libido
- middle waking insomnia
- hopelessness
- chronic suicidal ideation- no attempts
- poor concentration and memory
- moderate psychomotor retardation.

HOSPITALIZED
- 7 months in 1973

Treatment History

Prior episodes of treatment
- ECT 1973
- TCAs Amitriptyline 250 mg
- Tranylcypromine 80 mg – no help

Current treatment
- Sertraline 250 mg
- Geodon 80 mg
- Desoxyn 15 mg bid
- 6/03: add Strattera 120 mg
- 7/03: Provigil 200 mg bid
- Lexapro 20 mg (DC Sertraline)
- 9/03: Nortriptyline 100 mg
- 11/03 - 4/04 14
- ECT-improved
Past Treatment Hx (cont’d)

5/04
Relapsed – Sertraline 150 mg, Geodon 80 mg

7/04
10 ECT, Desoxyn 5 qid, Nortriptyline 75 mg. Improved

10/04
Relapsed -> anxiety total ECT 21 – duloxetine 120 Mg, ziprasidone 180 mg. - some improvement

4/05
Relapsed - severe emotional pain/anxiety quetiapine - 3 ECT

7/05
quetiapine 100 mg

TRMD – treatment

8/05 Begin phenelezine up to 90 mg – full remission.

4/06 – phenelezine 105 mg , quetiapine 200 mg – in remission

6/06 phenelezine, quetiapine (urinary retention) stopped for Prostate Ca surgery.

1/07 – phenelezine 120 mg, methylphenidate 10 qid, Seroquel 200 mg. remission.

9/06 phenelezine 105 mg, methylphenidate 1- qid remission

7/07 Eye surgery
Add methylfolate 7.5 mg

12/07 cruise to Panama
TRMD JP

2/08-11/09
Remission

11/09
Stopped methylphenidate – recurrence – restart

1/10
Remission 120 mg phenelezine, methylphenidate 20 mg bid, donepezil 10 mg.

1/11
Relapse depression – methylphenidate 20 tid – no help – phenelezine increased to 135 mg – remitted

TRMD JP Outcome

7/11
• Remitted phenelzine 120 mg. methylphenidate, 20 tid

8/11
• Severe OCD – some increased depression (had stopped methylphenidate) restarted

8/26/11
• Full remission, OCD improved (but present) phenelezine 120 mg, methylphenidate 20 bid, donepezil 5 mg.

1-2 days “depressed”/month – doing well.

2012
• Second brief relapse on phenelezine 120 mg and methylphenidate 20 mg bid – in both instances response returned in two weeks after phenelezine increased to 135 mg x 2 weeks, then could be returned to 120 mg/day with maintenance of response.

6/14
• Last seen — in remission OCD symptoms referred for CBT.

Stopping methylphenidate has resulted in 3 brief relapses.
Case 2

KH

• Male – 54 years old
• History of chronic depression for “13 years”
• History of hypomanic and mixed episodes-last episode 2 yrs ago
• History of alcohol, cannabis, and methedrine abuse- but not for 14 years
• Family:
  • mother: bipolar
  • maternal aunt: bipolar
  • father: alcoholic

CLINICAL

• Suicidal ideation - no attempts

HOSPITALIZED

• 5 times- last time - 2 years ago

STATUS

• Severely disabled since 1983

Past Treatment Hx (cont’d)

Two past courses of ECT 10 RX, 12 Rx. No help

Tranylcypromine (Parnate) 60 mg – 9 years ago (up to 180 mg)

Failed 3 SSRIs, Mirtazapine, Venlafaxine, Lamictal 175 mg, carbamazepine 1000 mg, methylphenidate, modafanil no help. lithium 1200 mg, still depressed.

In bed all day, lives alone, has a male friend.
TRMD – treatment

7/05 tranylcypromine up to 100 mg - no help

9/05 quetiapine up to 600 mg.

10/5 Augmentation with nortriptyline 100 mg, dextroamphetamine 20 mg bid – no help

Now what?

EFFECTIVE TREATMENT

1/06 clomipramine up to 250 mg – mood improved

3/06 recurrence of depression - quetiapine 100 mg

5/06 off clomipramine 5 days; switch to nortriptyline - depression increased — selegiline (patch 12 mg) - Now depression worse than in 14 years

Course of 12 ECT – no help

2/07 moderate depression

3/07 clomipramine 150 mg/VNS remitted

5/07 feels withdrawn - add Abilify 5 - 15 mg-improved

8/07 remitted

11/09 depression recurring on clomipramine 350 mg, lithium 900 mg, quetiapine 200 mg, VNS
Case 3

**NP**

**HISTORY**
- **Female, 51 years old (first seen in 2011)**
- Pakistani female physician (OB-GYN MD, retired 15 years ago) from Islamabad
- **Family:**
  - father bipolar depressed, ECT,
  - mother depression
- **Depressed mood for 2 years.**
  - Last happy in 2008 when daughter married and moved to US.

**CLINICAL**
- anxiety
- fearful
- panic
- not wanting to live
- feels hopeless in AM and totally alone, despite supportive husband and family.
- Indecisive: cannot decide what to wear, does not cook, but does exercise regularly at gym.
- low energy levels –feels a burden.
- total anhedonia.
- was shy and introverted.
- no history of mania/hypomania.

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**EFFECTIVE TREATMENT**

1/10
Still Depressed- pramipexole (1.0–3.0) mg added

Tired – added dexroamphetamine 10 mg tid

3/10 improved

6/11
“better than in 14 years” – clomipramine 225 mg., pramipexole 3.0 mg, dexroamphetamine 10 mg., tid plus VNS - no hypomanic or mixed episodes.

Living a full life, cooking (former chef), completed basic home nurse training, selling art cards.

Last seen 6/14 in full remission – living a full life.

Found to have Hep C, gallbladder stones to explain low energy. Symptoms remitted.
TRMD NP

Prior episode of depression after two miscarriages in 1993. Second episode 1997 - amitriptyline, fluoxetine and lithium, mirtazapine, risperidone 1.5 mg. for anxiety. Two months at duloxetine 120 mg plus aripiprazole not helpful.

Hospitalized for 5 days IV clomipramine followed by 225 mg po - no help.

Course of 7 ECT plus duloxetine and paroxetine - transient improvement then relapse.

TRMD – NP – past treatment

lamotrigine 200 mg, aripiprazole 30 mg, citalopram 40 mg.

10/10 – 9 ECT, ziprasidone 60 mg, lamotrigine 250 mg, citalopram 20 mg with no effect.

12/11 Seen in consultation – here for 4-6 weeks

Now what?
Considered MAOI treatment - but patient had forgotten about failure of duloxetine trial - so:

because of agitation/anxiety we started quetiapine 100-300 mg prior to visit.

Venlafaxine XR titrated rapidly to 300 mg /day, and

Pramipexole rapidly increased from 0.5 mg-3.0 mg. qhs as tolerated.

Patient seen in two weeks (travels - followed by resident).

Full Remission
some residual AM anxiety on venlafaxine 225 mg plus pramipexole 3.0 Mg.

Placebo response?

Two weeks later remission persists.

Follow up at 4 months: remission persists – but anxiety in AM continues

Follow up at 7 months: remission persists anxiety less mouth ulcers patient has GERD, but relates them to meds.

Email from Pakistan: anxiety gone remission persists ?? Lower Effexor XR to 150 mg - ? Taper off

Pt seen June 2012 had tapered off pramipexole, and reduced venlafaxine to 75 mg. No change reported by August 2012. No relapse or recurrence to present. Referred friend.
**Case 4**

- 56 yr old, married male, lawyer/musician
- Long standing treatment resistant depression, GAD and Etoh dep
- Referred to resident clinic 4/2012 by private psychiatrist for treatment after ECT and multiple medication trials failed to produce remission

**HISTORY**

- Chronic unrelenting depression and anxiety starting at 16 years old

**CLINICAL SYNDROME:**

- Amotivation
- Chronic
- Unrelenting dysphoria and SI without history of intent, plan or rehearsal
- Anhedonia
- Thought slowing
- Decreased concentration, libido, and early morning wakening
- No change in appetite and no psychotic sxs. Screening for mania and hypomania negative.

**TRMD PAST TREATMENT**

**SUD Hx** - First drink 17 y.o.
Abuse pattern at 23-24 year old, leading to 30 day rehab
Remained in full sustained remission
Binged 50-51
Stopped again, with brief periods of use.
Moderate within last few years and currently abstinent for 4 months.

**Past Treatment - CBT and therapy as a teenager**

- Early medication trials: desipramine, trazodone, sertraline 200mg, duloxetine 90mg, bupropion, aripiprazole 15mg, liothyronine, levothyroxine, modafinil 150mg, methylphenidate 20mg, lithium, olanzapine-fluoxetine combo, gabapentin 300mg BID, diazepam 10mg
TRMD PAST TREATMENT

Past Treatment - ECT x9 <25% improvement

4/2012
At time of referral- Regimen included fluoxetine 40mg, trazodone 100mg

5/2012
Added mirtazapine 15mg titrated to 30mg, pt had acute dysphoria, d/c all rx except for mirtazapine

5/2012
Added lorazepam 0.5mg bid, 1mg qhs, venlafaxine 100mg to mirtazapine 30mg

6/2012
Titrated mirtazapine 30 to 45mg, pt d/c venlafaxine, SE - started trial of quetiapine 50-100mg

TRMD-TL-Shaping Effective Regimen

6/2012
d/c quetiapine due to akathesia, added pramipexole 0.5mg, with rapid titration (increase by 0.5mg Q3 days)

7/2012
Mirtazapine 45mg, pramipexole 4.5mg

8/2012
added citalopram 20mg-40mg, however pt d/c as felt had no benefit

9/2012
clomipramine 50-100mg, d/c entire regimen due to MI.

nortriptyline 50mg in anticipation of bridging to MAOI during washout,

10/2012
Restarted venlafaxine 100-150, titrated to 300mg, restarted and titrated pramipexole to 4.5mg,

1/2013
increased Pramipexole to 5mg, added methylphenidate 10mg qd-bid
TRMD-TL-Effective Treatment

Current Outcome with regimen of
venlafaxine 300mg, pramipexole 4.5mg,
levothyroxine 150mcg, liothyronine
10mcg, lorazepam 0.5mg bid, 1mg qhs

Conducting musical pieces, finishing
incomplete Compositions from 1 decade
ago, Writing Multiple Instruction books
on Playing Piano, Anguish resolved
although he may have alexithymia

Had cardiac arrest, in M.D.'s office,
pacemaker implanted, new resident
discontinued pramipexole – depression-
full recurrence – pramipexole taken back
to 4.5 mg plus venlafaxine 300 mg q.d..
Full remission very productive writing
music compositions and books, smiling.

Last visit 6/14 – in full remission. Very
busy with job, music compositions.

Two Additional Cases

67 year old female

- chronic depression (persistent) over 12 years
- 12 ECT no help, some improvement with Abilify
- PPX – able to have sexual orgasm for first time since highest dose depressed.
- Able to laugh and joke.
- Full remission.

25 year old medical professional

- depressed 10 years
- 30-40 ECT no help
- MAOI selegeline at highest dose
  plus all SSRIs, SNRIs, TCA.
- Had plan to suicide with helium canister.
- Was told his case was “hopeless”.
- PHQ-9 score from 26 to 6 in 6 weeks. No suicide plan.
Dissecting Anhedonia

- DSM-5 definition: “Markedly diminished interest or pleasure in all or almost all activities most of the day, nearly every day (as indicated by either subjective account or observation)”
- Dopamine depletion - decreases anticipatory pleasure.
- Perception of effort required increases “can't do it”

Dopaminergic Function and Motivation
Treadway et al, 2011

- Rats with “knock-out” gene for dopamine.
- T-maze Left – “crappy” rat chow
- T-maze Right – bar press for luscious biscuit.
- Dopamine depleted = Left bar press too much work
- Dopamine restored = bar press for good stuff
- Dopamine = energy to obtain positive reinforcement.
- Dopamine – motivational/decisional hedonia (anticipatory) not steady state mood-like phenomenon
- Opioid receptors – experienced hedonia
Double Breaching Humpbacks 2013

Whose Dopamine Tone is Higher?
### Experience with Pramipexole (PPX)

**Dose tolerance/ requirements increases with age:**
- 30's: 0.5 - 2.5 mg
- 60's: 3.0 - 5.0 mg tolerated and required for response

Rate of increase balanced against time needed for response.

Nausea and sleepiness may remit over 7 days.

Give total dose at night – pts. have more SE and reject it when given during daytime.

Dose required for response/ tolerance highly variable

Does it work better with noradrenergic ADM's?

Patient failing stimulants may respond after PP

Patients may become more sensitive to dose, and discontinue over time – even without relapse – maybe dose can be decreased over time?

PPX is neuroprotective and neurorestorative – causes regrowth of DA neurons.

### Pramipexole

**Aiken CB, J. Clin Psychiatry – Pramipexole Review**

- reviewed 24 out of 500 articles: large effect size (.6 - 1.0) in the treatment of both bipolar and unipolar disorder.
- Low rate of manic switching.
- Pooled discontinuation rate 9%
- Neuroprotective and beneficial effects on sleep architecture

**Side Effects**

- sleep attacks
- compulsive behaviors and pathological gambling – reported in Parkinson, restless legs syndrome and psychosis in psychiatric and Parkinson's disease.

**Personal Experience**

- Dose tolerance seems higher as age is higher.
- Most TRMD responders at 3-5 mg given qhs. < 35 more SE nausea, profound tiredness, response as low as 0.5 mg. 84 year old patient – response peak a 5.0 mg qhs.
What’s a Downside:
DAWS (Dopamine Withdrawal Syndrome)

First reported in Parkinson’s (n=40, 19%)
Rabanak CA and Nierenberg MJ, 2010

Subsequent reports:

Impulse control problems
Anxiety
Fatigue
Insomnia
Autonomic symptoms

Especially prevalent in patients with impulse control problems – slow withdrawal of dopamine agonists

MAOIs in CPT3 – Prevention of Recurrent Depression with CT and Medications
(Rush, Penn, Vanderbilt)

452 – Patients with third episode of recurrent depression.
Half CT plus medication; Half medication need to attain remission

41 patients received MAOI
39.5% remitted

35 patients relapsed in Continuation and received MAOI
37% remitted

12 recurred and received MAOI in maintenance phase.

Of 88 patients, one Serious Adverse Event – Soy Sauce induced hypertensive reaction, survived.
**Summary**

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<tr>
<th>Six cases of Treatment Refractory Depression</th>
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<td>• failure of at least 3 NGA plus augmentation, TCA trial, and at least two ECT trials - are presented who received a sustained recovery</td>
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<td>• over 2-4 years in 4 cases</td>
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<tr>
<td>• 12 months and counting in one case</td>
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<td>• one case just responded</td>
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<tr>
<th>One case responded to phenelezine plus methylphenidate and</th>
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<tr>
<td>• five responded to pramipexole (PPX) plus either venlafaxine or clomipramine and methylphenidate.</td>
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<th>Two patients may have experienced decline of anxiety severity.</th>
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<th>It appears that dopamine active medications are limited to a few and may be likely to be effective in TRMD.</th>
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<td>• They seem to increase pleasure seeking behavior more an other ADMs - This may be why they are particularly effective – other commonly used antidepressants target serotonin (SSRIs), or norepinephrine (SNRIs) or both, but not dopamine (DA) function.</td>
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