DOPAMINERGIC TREATMENT OF TREATMENT REFRACTORY MOOD DISORDERS

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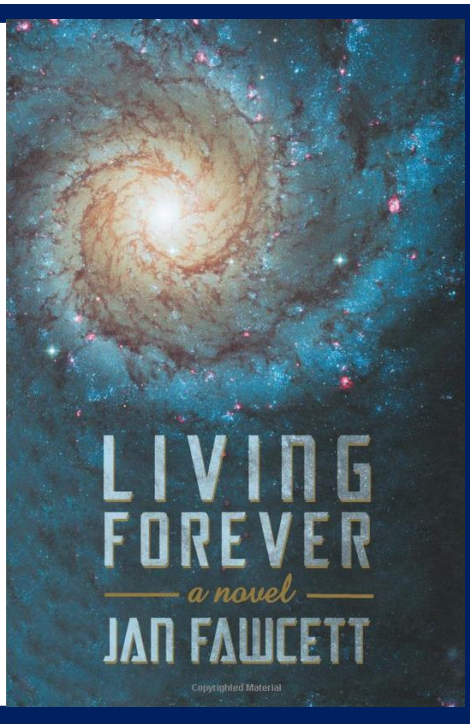
Conflicts:

More enjoyment than facts …

…on Amazon!



ABBREVIATIONS

BPD	Borderline Personality Disorder
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECT	Electroconvulsive therapy
MAOI	Monoamine oxidase inhibitors
MDD	Major depressive disorder
NGA	New generation antidepressants
NNT	Number needed to treat
OCD	Obsessive-Compulsive Disorder
PPX	Pramipexole
SNRI	Serotonin–norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
SUD	Substance use disorder
TCA	Tricyclic antidepressants
TRD	Treatment-resistant depression
VNS	Vagus nerve stimulation

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*

Treatment step 1 – citalopram	36.8 % remission
Overall Remission Rates steps 1-4	67%
Treatment Resistant	33% after four steps of treatment

BUT

Four Month Recurrence rates step 1-4	40.2%- 71%
Recovery rates	67% x 60% = 40.2% "Recovered" at 4 months

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 + flouxetine 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

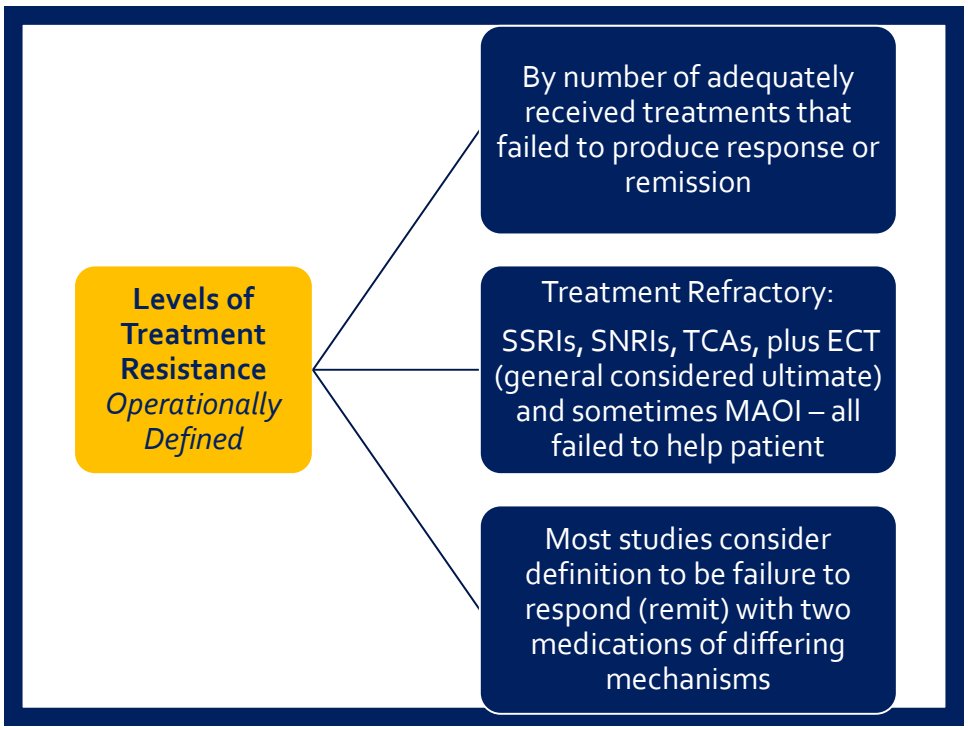
Dell'Osso et al, 2013

- Usual NNT for psychiatric medications NNT 3-6
  100 / (remission rate – 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?

Bupropion	Aripiprazole (Abilify)	Modafinil	Stimulants	Pramipexole (PPX)
•22% affinity for dopamine transporter •very weak - common use. •Two studies – did not exceed placebo when added to SSRIs	•partial dopamine agonist – augments ADMs.	•unknown full mechanism, some increase in dopaminergic function.	•Dextro- amphetamine, Methylphenidate – increase by surge	•D_3 autoreceptor agonist – increases dopamine tonic levels. •Was used in Parkinson's Disease for motor symptoms – 2nd to loss of dopamine neurons. •Was found to benefit depression (particularly ***anhedonia*** - inability to pursue and enjoy usual pleasures). •Found effective in depression without Parkinson's Disease (Aiken C., 2007) •PPX is off –patent (was Mirapex) – not marketed.

- 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)



Case 1

JP

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)*

JP

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

JP

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

JP

2/08-11/09
Remission

11/09
Stopped methylphenidate – recurrence –restart

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

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

TRMD JP Outcome

7/11
- Remitted phenelizine 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) phenezine 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.

Stopping methylphenidate has resulted in 3 brief relapses.

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

JP

Case 2

KH

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)*

KH

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

KH

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

↓

Back to clomipramine- 250 mg- this time depression stabilized

→ VNS implantation

→ 11/06
250-300 mg.

→ 1/07
depression stabilized – has VNS implant.

↓

2/07
moderate depression

→ 3/07
clomipramine 300 mg/VNS remitted

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

→ 8/09
remitted

↓

11/09
depression recurring on clomipramine 250 mg, lithium 900 mg, quetiapine 200 mg, VNS

KH

EFFECTIVE TREATMENT

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

Tired – added dexroampheidamine 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.

Had some recurrence of decreased energy – reversed with increase of pramipexole to 4.0 mg.

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

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.

KH

Case 3

NP

NP

- **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

HISTORY

- 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.

TRMD NP

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

NP

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?

NP Effective Treatment

NP

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)*

NP Outcome

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.

NP

Case 4

TL

TL

- 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

TL

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, trazedone, 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

TL

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 methylphenidte10mg qd-bid

TL

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	25 year old medical professional
• 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.	• 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.

- 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

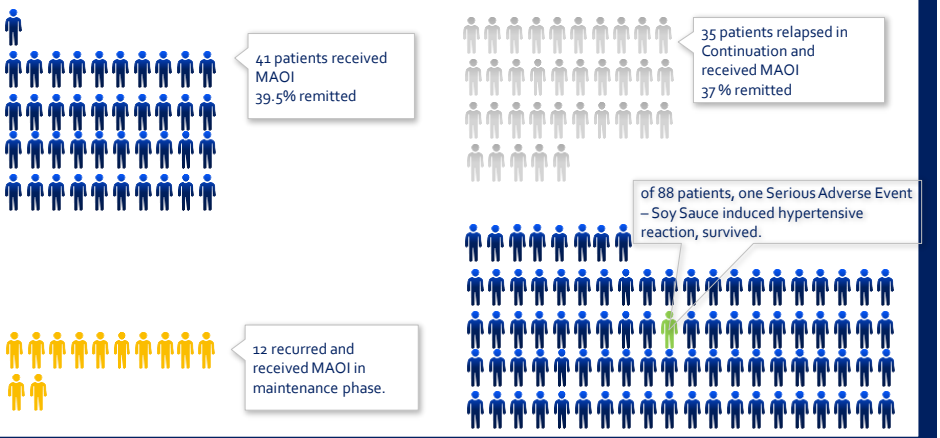
Subsequent reports:
Pondal et al 2013, Edwards MJ, 2013

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



Summary

Six cases of Treatment Refractory Depression

- failure of at least 3 NGA plus augmentation, TCA trial, and at least two ECT trials - are presented who received a sustained recovery
  - over 2-4 years in 4 cases
  - 12 months and counting in one case
  - one case just responded

One case responded to phenelezine plus methylphenidate and

- five responded to pramipexole (PPX) plus either venlafaxanie or clomipramine and methylphenidate.

Two patients may have experienced decline of anxiety severity.

It appears that dopamine active medications are limited to a few and may be likely to be effective in TRMD.

- 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.